Crizanlizumab, Voxelotor, and L-Glutamine
for Sickle Cell Disease:
Effectiveness and Value

Evidence Report

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Voxelotor (OXBRTYA®, Pfizer) was withdrawn from the market on September 25, 2024.

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For a complete list of stakeholders from whom we requested input, please visit:
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List of Acronyms Used in this Report

AE	Adverse event
ACS	Acute chest syndrome
AKI	Acute kidney injury
BPI	Brief Pain Inventory
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
ED	Emergency department
FDA	Food and Drug Administration
GDP	Gross domestic product
HB	Hemoglobin
HR	Hazard ratio
IQR	Interquartile range
ITT	Intent-to-Treat
LS	least squares
LY	Life year
MCC	Major complications and comorbidities
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
No.	Number
NS	Not significant
NR	Not reported
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QOL	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SCD	Sickle cell disease
SF-36	36-Item Short Form Survey
TEAE	Treatment-emergent adverse event
US	United States
USPSTF	United States Preventive Services Task Force
VOC	Vaso-Occlusive Crisis
WAC	Wholesale acquisition cost

Executive Summary

Background

Sickle cell disease (SCD) is a broad term referring to a group of inherited disorders carried by the beta (β) allele of the hemoglobin (Hb) gene. It is characterized by abnormal hemoglobin polymerization during deoxygenation resulting in sickle-shaped erythrocytes (red blood cells [RBCs]). The incidence of SCD is estimated at 300,000 to 400,000 live births globally per year. In the United States (US), the current best prevalence estimate is approximately 100,000 individuals with SCD, although comprehensive surveillance and reporting is lacking and the exact number of cases in the US is unknown.[2]

Clinical manifestations of SCD derive from at least three different pathophysiologic mechanisms: the loss of deformability of the RBC leading to vascular obstruction and ischemia; a shortened lifespan of the RBC leading to both intravascular and extravascular hemolysis; a sticky RBC surface increasing adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions.[3]

Recurrent acute pain crisis, or vaso-occlusive crisis (VOC), is one of the most prevalent manifestations of SCD. Patients also experience significant acute complications such as acute chest syndrome, serious infections, stroke, renal necrosis, and priapism.[4] Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality.[4] Resultant health care costs are high, with the total health system economic burden of SCD estimated at $2.98 billion per year in the US with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[5]

The impact of SCD on quality of life (QOL) is complex and affects both patients and their caregivers in many ways. In addition to the health-related burden of disease, many other factors further diminish QOL. The lack of treatment options, discrimination, stigma around the need for chronic pain management, disruption of family and social activities, missed school and/or work all combine to make living with SCD very difficult.[6]

We heard from both patients and clinicians that the picture of "baseline" or "usual" care for patients with SCD is highly variable. Deep dysfunction in care is driven by poor coordination within provider systems and by barriers to access that arise from a broad range of factors including systemic racism, uninformed clinicians, poverty, and insurance systems poorly designed to coordinate coverage for patients with multi-system chronic conditions.

Until recently only three specific interventions were considered helpful for SCD: stem cell transplantation, chronic transfusion with packed RBCs, and hydroxyurea.[7] Chronic transfusion is generally used for primary or secondary stroke prevention; hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises, and in those with a history of ACS or severe anemia.[8] Acute pain crisis may be managed with pain medications including opioids, and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments.[8]

Within the past several years several new options have gained regulatory approval in the US. L-glutamine (Emmaus) is a precursor of nucleic acids and nucleotides that play a key role in the regulation and prevention of oxidative damage to red blood cells.[9] It was approved by the US Food and Drug Administration (FDA) on July 7, 2017 to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older. Crizanlizumab (Novartis AG), is a humanized monoclonal antibody that binds to P-selectin. P-selectin is expressed on the surface of endothelial cells and platelets and it is thought that blockage could reduce the static adhesion of sickled RBCs thus reducing vaso-occlusion and inflammation.[10] It was approved by the FDA on November 15, 2019 to reduce the frequency of vaso-occlusive crises in adults and pediatric patients ages 16 years and older with SCD. Voxelotor (Global Blood Therapeutics, Inc.) is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissociation curve.[11] Voxelotor was approved by the FDA on November 25, 2019 for the treatment of SCD in adults and pediatric patients 12 years of age and older.

Insights Gained from Discussions with Patients and Patient Groups

"SCD is long overdue for a treatment and cure. It is buried in years of racial discrimination and to this day health care professionals treat based on assumptions not science. We need new drugs and treatments. [It's] about time we matter." – Parent of an individual living with SCD

An All-Encompassing Condition

Patients, family members, clinicians, and other members of the sickle cell community conveyed that it is hard to imagine a condition that ravages people's lives more than SCD. It is a danger to minimize the impact of the condition by reducing it to pain crises, or even to the better known acute and chronic organ effects. Pain crises are, of course, horrible to experience, and their accumulated impact over many years has effects on physical and mental health as well as the potential risks associated with opioid treatment[12] In addition, the range of acute adverse effects of the condition includes almost every organ system, with strokes, ACS, and other life-threatening events a constant threat. These acute effects contribute to long-term risks for additional major organ dysfunction such as congestive heart failure and liver failure.[13]

But while these acute and long-term clinical harms are legion, patients and others emphasize that there is truly an all-encompassing biopsychosocial impact of SCD that is hard to capture, even by adding up one by one the multitude of organ system effects. There is fatigue, there is anxiety and depression, there is a hopelessness that has haunted patients with SCD. The condition presents challenges at home, school, work, and social relationships.[14] People with SCD often end up on formal disability programs, which unfortunately carries its own stigma. The cumulative effect of all these effects can be staggering.

"SCD is extremely unpredictable, even for the most aware patient. There is such a stigma that I feel from having this disease, wanting to do so much and contributing to society and yet I am limited from achieving many of my hopes and dreams." – Patient living with SCD

This is not to say that people with SCD are unable to function at a high level in society, but that the challenges and the barriers are extraordinary. One of the most important perspectives we learned from the SCD patient community and clinicians was that SCD remains a misunderstood, marginalized, condition. To fully appreciate the potential benefits of new treatments, a broad appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments.

Stigma and Limitations on Daily Life

Patients with SCD may appear healthy. An outward appearance of wellbeing can present additional barriers to appropriate care and contribute to social stigmas surrounding the disease. A general lack of awareness about the disease among nurses, hospitalists, and society at large means that healthy-looking patients suffering from an acute pain crisis, ACS, or other SCD-related complication may not be taken seriously. Patients presenting at the ER may be made to wait longer before receiving attention.[15,16] One particularly jarring anecdote that was recorded in the FDA's *Voice of the Patient* report described a child who was sent back to class by the school nurse after suffering a silent infarct because he was "deemed unruly."[6] We also heard patient testimony of young men being called perverts because they were experiencing priapism.

> *"Day to day is hard. [We] are in pain a lot and our energy levels are low. We just want to be treated like the next. We are not lazy, we want fairness."*
> *– Patient living with SCD*

The appearance of health, coupled with a lack of SCD awareness in patients' broader communities, can lead to ignorant judgments of character. Patients who are unable to participate in their daily commitments at work or school due to unsurmountable fatigue, pain, or other complications, may be accused of laziness or be subject to bullying. Both children and their caregivers felt SCD challenged their ability to perform well in school and work[14] Chronic daily pain, fatigue, and the sudden onset of acute pain crises increase absenteeism, make it difficult to concentrate, disrupt school and social interactions and create a lot of stress and anxiety. SCD can cause neurocognitive impairment; some patients have reported difficulty remembering tasks, retaining what they learn in school, and difficulty staying engaged and focused on school activities.[17-19] Some children reported frustration and social isolation from limitations on their ability to participate in physical activities, travel on long flights, play outside in cold weather, or swim in unheated water. Although SCD is an inherited condition, a lack of societal awareness about the disease leads some patients to hide their diagnoses so that their peers will not misperceive them as contagious.

> *"My son feels very isolated by sickle cell, and I know he thinks he prevents our family from doing many things because so much of the year we have to stay indoors. He loves to visit places where the temperature is nice and he can easily be outside." – Parent of an individual living with SCD*

Family members described the tremendous responsibility of caregiving, including the need to leave the work force to provide care for their loved one while facing the impact of lost wages and significant out-of-pocket expenses. Adult patients reported difficulty in maintaining employment

because of frequent, unexpected, or prolonged absences due to acute SCD-related events. Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation. We heard from a number of patients that mental health issues such as depression, anxiety, and suicidal thoughts are common; such statements are corroborated in the clinical literature.[12,14,20]

Racial Bias

"To improve health care access, the sickle cell community is faced with the awesome task of trying to rewrite the dominant narratives about their patients whose genetic disease marks them in the United States as quintessentially black. This narrative presumes that sickle cell patients are socially dysfunctional, dependent on narcotics, and poorly educated or, worse, uneducable. Knowing only a patient's race or ethnicity, even a well-meaning doctor may make presumptions that influence how he or she communicates with and medically treats a patient."[1] – Rouse, 2009

We heard consistently, from patients, family members, clinicians, and other members of the sickle cell community, that the experience of living with SCD and all aspects of its treatment are mired in racism. Although SCD affects individuals of different races and ethnicities, it has historically been viewed in the US as a "black disease."[1,21] Racism, implicit or otherwise, presents devastating obstacles to care in what is already a debilitating and frequently lethal condition.[1]

We heard frustration from the sickle cell community about the lack of investment in research or comprehensive treatment centers that might increase access to better treatment, improve health outcomes, and reduce other disparities faced by SCD patients and their families. Historically, SCD has been underfunded, with no breakthroughs or developments in two decades. Although the populations of patients

"Consider the fact that we get stigmatized at regular ER hospitals, consider that our bodies work 3 times more than a regular human being, consider that this nation doesn't make sickle cell as a top priority as cancer, leukemia, or AIDS/HIV." – Patient living with SCD

living with other severe hereditary conditions such as cystic fibrosis are significantly smaller than that of SCD, these conditions often receive greater funding for research and treatment. Cystic fibrosis, for example, affects approximately 30,000 people in the US (versus about 100,000 with SCD) and receives 7-11 times the amount of funding per patient.[15,22,23] Structural racism, as well as implicit bias, affect the allocation of resources toward research, health care delivery, and quality improvement.[24,25]

Pain Relief

Racial bias and treatment disparities are glaringly obvious in the dispensing of analgesics for patients with SCD. Patients who present at emergency rooms in crisis are treated with suspicion.[1,15,26-29] We heard from some patients that they get dressed up in professional attire while in crisis before going to the ER in an effort to avoid categorization as drug seeking. Patients expressed a hesitancy to reveal any familiarity with pain regimens they know to be effective out of fear they would be denied relief or labeled as an addict. We heard that many adult patients have an advocate accompany them on visits to an emergency department to increase their chance of receiving appropriate treatment for pain.

Racial bias in the prescription of pain medications has been well documented. A survey of more than 100 physicians who care for patients with SCD suggested that provider attitudes toward opioid addiction can have negative implications for patients, including undertreatment of pain and discrediting a patient's report of pain severity.[15,27] Furthermore, a 2014 study of attitudes toward patients with SCD among 215 emergency department providers (nurses and physicians) found that relative to physicians, who have less frequent and shorter interactions with patients, nurses had greater levels of negative attitudes toward SCD patients; nurses expressed more frustration in caring for patients, estimated a higher prevalence of opioid addiction among patients with SCD, and reported less unease with the ways in which their colleagues treated patients.[15,28]

The ongoing opioid crisis has further complicated patients' ability to access pain medicine, as

"Most of us aren't coming into the hospitals until the pain is at ridiculous levels because we HATE feeling judged all the time. I don't know what these docs are being taught, but it seems compassion ain't part of the curriculum! […] Most times when describing my pain I don't look at them at all, because if I do and I see that apathetic or judge-y, doubtful look on they face it makes me instantly regret coming in. It's hard because they want you to give eye contact, speak clearly and be so detailed, all of which are incredibly hard when you in pain […]. I've felt like I had to put on a show when I was younger because if I said I'm a 8, 9, or 10 without crying or writhing in pain, they'd never believe me. It was obvious they didn't believe it by how long it would take me to get my medication, or all the tests I'd be forced to take before getting anything for pain." – Patient living with SCD

doctors have grown increasingly wary of over-prescribing addictive therapies. Many state laws, payer coverage policies, and hospital protocols follow "one size fits all" approaches to pain management, which limit dosing or cease dispensing after a predetermined period of time, irrespective of whether an individual's pain is adequately managed. The Centers for Medicare & Medicaid Services recently issued a policy to recommend that Medicare beneficiaries with SCD be

exempt from opioid safety restrictions; similar exemptions have been recommended in some state Medicaid programs, although such policies will not improve patient access if provider attitudes do not also change.[15,30,31]

Lack of Specialists & Competent Treatment

Patients lamented that SCD education and awareness among clinicians, even among hematologists, is severely lacking. Patients commonly receive care from generalists, emergency nurses, and hospitalists, who may be less equipped to help them manage their disease.[15,32,33] We heard repeated concerns that there were not enough doctors and other medical providers who are adequately trained in the management of SCD, particularly for adults. A national survey of over 3,000 family physicians revealed that only 20% of respondents felt comfortable treating SCD.[32,33]

Clinical experts and patients alike commented that incompetent care can be catastrophic; we heard several anecdotes about deaths that might have been prevented had the patient received care from a more knowledgeable provider. Patients are conscious of the deaths and irreversible damage that results from long wait times in the ER, as well as the increased mortality from events that occur in the hospital; they reported feeling intense anxiety and stress about going to the hospital, sometimes delaying or avoiding seeking necessary care. We also heard that some individuals experience post-traumatic stress disorder following severe episodes of illness.

"Too often Sickle Cell Patients are marginalized, treated with stereotypical idealism and inherent bias that ultimately leads to them avoiding going for help or simply not receiving it in their greatest time of need, during the vaso-occlusive crisis. This leads to many damaging side effects including death but more so the damage taking place in their bodies while they are lingering in an untreated state of ongoing necrosis taking place throughout their bodies!" – Patient living with SCD

Among non-specialist providers, we heard there is often the misperception that SCD is a pain condition. This over-simplification can lead to inappropriate care of the disease's many complications. In the ER, treatment with fluids, oxygen, and other medicines may be lacking and patients may be not be appropriately triaged. One caregiver,

"Finding a great doctor that knows information about sickle cell is finding a needle in a haystack" – Patient living with SCD

who was not a trained clinician, told us about needing to adjust a patient's oxygen level while in the

hospital out of fear that inadequate attention from the attending providers would prove fatal to the patient.

While the management of pediatric patients with SCD has improved dramatically in recent years, the transition from pediatric to adult care presents a major risk for many patients. There is a significant shortage of adult care providers with the requisite knowledge and skill set. Patients described the difficulty they faced trying to navigate a very different system of care, and recounted a worsening of health as a result of limited access to multi-dimensional care. Indeed, there is a sharp increase in mortality during the transition from pediatric to adult care.[34,35]

This problem is magnified in smaller cities, towns, and rural areas, where patients report needing to travel several hours to see a specialist, participate in a clinical trial, or access treatment through a compassionate use programs. Patients were anxious that the retirement of a community's only specialist would lead to a spike in SCD mortality. A retired specialist from California, Dr. Keith Quirolo, provided some sobering statistics about the severe shortage of sickle cell hematologists: in the state of California, where Dr. Quirolo used to practice, there are only about five physicians who specialize in the treatment of SCD for an estimated 7,000 residents living with the condition.[32]

Attitude toward New Therapies

There is consensus in the SCD community about the dire need for disease-modifying drugs. Over the past several years, few treatment options aside from analgesia were available. Barriers to accessing and utilizing the few available options, such as pharmaceutical-grade L-glutamine and hydroxyurea are many; these include insufficient payer coverage, a lack of pharmacies that stock these drugs, a lack of awareness among providers about L-glutamine (and reluctance to prescribe it), and patient fears and/or intolerance of undesirable side effects (e.g., running to the bathroom from gastrointestinal side effects of L-glutamine; hair loss or infertility from hydroxyurea). In addition, patients pay out of pocket for supplements commonly recommended for SCD, such as zinc, vitamin B12, chlorophyll, iron, and folic acid.

"The quality of life for most Sickle Cell Patients is a life of extreme suffering from pain and rejection of medical care. We are stigmatized as drug seekers because there is hardly any tools a care provider can offer us but pain killers. Life is painful and frustrating, and we have few choices in our options for care." – Patient living with SCD

There is cautious optimism about the promising pipeline of therapies, particularly gene therapies, that may soon become available. Nevertheless, patients and families worry about being able to afford expensive new drugs and are concerned that high drug prices may cause insurance policies to implement barriers to access. Patients are concerned that doctors will not know enough about the new therapies

to be willing to write prescriptions for them. Patients also wonder whether they will be eligible for treatment with these new treatments. We heard from some patients that they fear they will be too old or have too much organ damage to be candidates for gene therapy.

Finally, stakeholders emphasized the importance of multidisciplinary care. New therapies need to be integrated into treatment plans that care for the whole patient.

Comparative Clinical Effectiveness

To inform our analysis of the clinical effectiveness of crizanlizumab, voxelotor, and L-glutamine in the treatment of SCD, we sought evidence related to each of these therapies in comparison with optimal usual care (as estimated by the placebo arm of the controlled trials). We did not attempt to compare the interventions to each other, as these therapies may have a complementary role in the management of SCD. Our review focused on clinical benefits (i.e., mortality, acute pain crisis, organ damage, and quality of life), as well as potential harms (drug-related adverse events [AEs]). Key findings are summarized by drug in the sections that follow.

Clinical Benefits of Crizanlizumab

Evidence on crizanlizumab was derived from the SUSTAIN trial.[36] This study was a Phase II, placebo-controlled trial that randomized 198 individuals with SCD to 5.0 mg/kg of crizanlizumab (n=67), 2.5 mg/kg of crizanlizumab (n=66), or placebo (n=65). As crizanlizumab was approved at the higher dose (5.0 mg/kg), efficacy data pertaining to the low-dose arm of SUSTAIN was not summarized in this review.

The SUSTAIN trial's primary endpoint was the annual rate of sickle cell-related pain crises, defined as acute episodes of pain that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug.[36] Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered to be crisis events.

Compared to optimal usual care alone (i.e., placebo), patients treated with crizanlizumab experienced fewer acute pain crises per year (median annualized rate of 1.63 vs. 2.98 in the crizanlizumab and placebo groups, respectively).[36] A time to event analysis suggested that crizanlizumab reduced the risk of a first acute pain crisis following treatment initiation by 50% (Hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.33 to 0.74). Patients treated with crizanlizumab had a numerically lower annual rate of days hospitalized, although this outcome did not reach statistical significance. Crizanlizumab did not improve quality of life, as measured in the study.

Harms of Crizanlizumab

There were three deaths among patients treated with crizanlizumab in the SUSTAIN trial, although none were considered by the investigator to be related to study therapy.[36] Serious adverse events (SAEs) that occurred in patients treated with crizanlizumab included pyrexia (3%) and influenza (5%). In addition, there was one life-threatening case of anemia and one intracranial hemorrhage reported in the low-dose crizanlizumab group. Fewer patients discontinued treatment due to an AE in the crizanlizumab group (2%) than the placebo group (5%). The most commonly reported AEs included back pain, nausea, arthralgia, and pyrexia. The prescribing information for crizanlizumab includes warnings for infusion-related reactions and interference with automated platelet counts (i.e., platelet clumping).

Clinical Benefits of Voxelotor

Our review of voxelotor was informed by the HOPE trial.[37] This study was a Phase III, placebo-controlled trial that randomized 274 individuals with SCD to receive a once-daily oral dose of 1500 mg of voxelotor (n=90), 900 mg of voxelotor (n=92), or placebo (n=92). As voxelotor was approved at the higher dose (1500 mg), evidence pertaining to the low-dose arm of HOPE was not summarized in this review.

The HOPE trial's primary endpoint was hemoglobin response, defined as a 1 g/dL change in hemoglobin.[37] At week 24, 51% of the voxelotor group and 7% of the placebo group had a response (mean change 1.1 g/dL vs. -0.1 g/dL for the voxelotor and placebo groups, respectively; p<0.001). Patients treated with voxelotor also had significantly greater reductions from baseline in indirect bilirubin levels and percentage of reticulocytes, suggesting reduced levels of hemolysis (destruction of RBCs).[37]

Red-cell transfusions were administered to 33% of voxelotor patients and 25% of placebo patients (statistical testing not reported); the majority of these transfusions were due to acute pain crises.[37] The incidence of SCD-related acute pain crisis was evaluated as a secondary endpoint and did not differ between trial arms.[37] Voxelotor did not improve quality of life, as measured in the study.

Harms of Voxelotor

There were four fatal AEs in the HOPE trial, two of which occurred in patients treated with voxelotor; none of the deaths were determined to be related to the trial drug.[37]

Serious treatment-emergent AEs that were deemed related to treatment were reported in 3% of patients treated with voxelotor and 1% of placebo-treated patients; 9% of patients in the voxelotor group discontinued therapy due to AEs compared to 4% of patients in the placebo group.[37] The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache. The FDA

prescribing information for voxelotor includes warnings for hypersensitivity reactions and interference with laboratory tests for quantification of hemoglobin species.

Clinical Benefits of L-Glutamine

The primary source of evidence for our review of L-glutamine was the Phase III, placebo-controlled trial from Niihara et al. (2018);[9] The study randomized patients with SCD to receive a twice-daily dose of L-glutamine (0.3 g per kilogram up to 30 g per day) or placebo.[9]

Statistically significant differences in the number of SCD-related acute pain crises were reported in the Phase III trial, with a median count of 3.0 in the L-glutamine group and 4.0 in the placebo group (p=0.005).[9] These results may be biased due to the imputation methods that were used to account for a high and differential rate of early trial discontinuation. The FDA conducted several sensitivity analyses and ultimately concluded that L-glutamine likely offers some benefit, but the degree to which it reduces acute pain crises is sensitive to the analysis approach taken.[38]

At Week 48, the median number of SCD-related hospitalizations was lower in the L-glutamine group than the placebo group (p=0.005).[9] Quality of life was not evaluated in the Phase III study.

Harms of L-Glutamine

A total of three treatment-emergent deaths occurred in patients treated with L-glutamine during the Phase II and Phase III trials. The investigator did not determine these deaths to be related to the study drug, but the FDA noted there was insufficient data available to be able to categorically rule it out.[38]

SAEs that were deemed to be related to L-glutamine included hypersplenism (n=1), sickle cell anemia with crisis (n=1), abdominal pain (n=1), and chest pain (n=1); 3% of patients treated with L-glutamine discontinued treatment due to AEs compared to 1% of patients in the placebo group.[38] The most commonly reported AEs included constipation, nausea, vomiting, headache, pain in extremity, back pain, and noncardiac chest pain.

Uncertainty and Controversies

Generalizability of Patient Populations Studied

Although patients with SCD may experience their first acute pain crisis or other important clinical manifestation before their first birthday, very few children, and no infants were included in these studies. The youngest ages included in the available studies were 16 years for crizanlizumab, 12 years for voxelotor, and 5 years for L-glutamine. These inclusion criteria make it difficult to generalize results to pediatric patients with SCD, all of whom will likely experience anemia and/or pain.

Patients in these trials differed by factors other than age. The definition of acute pain crisis, baseline hemoglobin levels, and baseline number of pain crises also differed across studies. Because the majority of enrolled patients had the HbSS genotype there are insufficient data available to determine whether the risk/benefit profile of these new therapies differs across different genotypic and phenotypic subpopulations.

All of these factors are important as clinicians make prescribing decisions.

Generalizability of Results Based on "Optimal Usual Care" Control Arms

It is evident from input from clinical experts and patient advocates that the quality and intensity of "usual care" delivered to patients in the control arms of the clinical trials we reviewed was far better than the usual care received by the vast majority of patients with SCD in the US.

How this difference in "usual care" affects the magnitude of the relative benefits of treatment with these new interventions is difficult to judge. It is difficult to know whether the magnitude of benefit would be greater in a real-world clinical setting where usual care has not been maximized or whether maximizing baseline care is a prerequisite for maximizing the benefits of these new therapies. What is certain, however, is that the introduction of new, effective treatments for SCD serves as an opportunity for the overall care of patients with SCD to be re-imagined and improved from top to bottom.

Quality of Life

None of the trials demonstrated an improvement in quality of life based on the instruments chosen by the investigators and studies for L-glutamine did not include any measures of quality of life. It is unclear if this finding is due to the instruments used in the trials or if these new therapies provide some benefit to patients but not at a level that improves their quality of life. The BPI, SF-36, and EQ-5D-5L are all general quality of life instruments that are used across a number of different health conditions and were used in studies of both crizanlizumab and voxelotor. The HOPE trial for voxelotor also used the Sickle Cell Disease Severity Measure (SCDSM), an SCD specific instrument. This instrument was not able to detect an improvement in quality of life in the HOPE trial. For historic context treatment with hydroxyurea has been shown to both decrease pain crises and improve quality of life. Since decreasing pain crises should increase quality of life there continues to be important uncertainty about whether these new therapies impact quality of life or whether the instruments used in the clinical trials were not sufficiently sensitive to detect that improvement.

Drop Out

All studies reviewed had significant rates of attrition. If drop-out rates in real-world practice are even higher than those seen in the clinical trials, which is likely, it is possible that the magnitude of longer-term benefits seen with treatment in the studies would not be realized. Some clinical

experts also expressed concern that sudden withdrawal or noncompliance with voxelotor might result in a high rate of hemolysis, potentially worsening vasculopathy. Other experts reported relatively poor compliance with L-glutamine in some of their patients due to the dosing regimen. There is currently no information on how to safely discontinue any of these medications should that be necessary.

Durability of Benefits

At this time there are no data on the durability of the effects observed in the clinical trials. We do not know if positive effects will continue to be seen in patients over the course of several years or a lifetime.

Long-Term Safety

All three therapies are relatively new, each with a novel mechanism of action. We lack long-term safety data and it is possible that undetected safety events will be identified over time or that the benefit/risk profile might change over time. There is also uncertainty as to which subpopulations of patients may have an increased risk of AEs.

Combination Therapy

From a clinical perspective these therapies might be used in various combinations with hydroxyurea, chronic transfusion, and each other as they all have different mechanisms of action. Without data to help clinicians understand the optimal way to combine therapies, there is uncertainty about whether combination therapy represents an optimal approach for some patients or whether combining therapies will increase AEs (and costs) without commensurate clinical benefit.

Impact of Therapy on Acute and Chronic Outcomes and Mortality

The full clinical benefit of these therapies is unclear. Although acute pain crises have been associated with an increased risk of other acute and chronic conditions, it is not possible to know at this time if treatment with crizanlizumab will decrease the rates of these conditions or will improve overall survival in treated patients. For all three treatments reviewed in this report there are reasons to be optimistic about beneficial long-term effects, and our economic model has made favorable assumptions about the linkage between short-term outcomes and longer-term health benefits. Nevertheless, there remains significant uncertainty about the true magnitude of the benefits that patients will receive.

For patients treated with voxelotor there is an additional concern that adds to the uncertainty about long-term benefits. The trial demonstrated that although hemoglobin levels increased with treatment, the rate of pain crises did not decrease. There was also a numerically higher rate of

transfusion in the treated group compared to the placebo group, a puzzling finding given that voxelotor did increase average hemoglobin levels, but one most likely due to a higher rate of pain crises among treated patients. As with crizanlizumab, there are no data on whether treatment with voxelotor will improve acute or chronic complications of SCD or increase survival.

For patients treated with L-glutamine an additional layer of uncertainty is created by the significant differential drop-out rate that saw treated patients dropping out at a higher rate than patients receiving placebo. Furthermore, the impact of L-glutamine on pain crises differed based on the imputation method used to account for those patients who dropped out. As with crizanlizumab and voxelotor, there are no data on whether treatment with L-glutamine will improve acute or chronic complications of SCD or increase survival.

Summary and Comment

Using the ICER Evidence Matrix (Figure 4.1.), we assigned independent evidence ratings for crizanlizumab, voxelotor, and L-glutamine, each compared to optimal usual care as defined by the placebo arm of their respective clinical trials.

Crizanlizumab versus Optimal Usual Care

The primary source of evidence for our evaluation of crizanlizumab was a single Phase II trial (SUSTAIN).[36] Compared to optimal usual care, crizanlizumab statistically significantly reduced the rate of acute pain crises in patients with SCD and prolonged the time to first and second crisis. Patients treated with crizanlizumab experienced approximately one fewer pain crisis per year, from approximately 3 in optimal usual care to approximately 2 with treatment.

Although rates of acute pain crises were reduced, statistically significant improvements in the annual rate of days hospitalized and quality of life were not observed in the SUSTAIN trial. Questions about safety also remain. Crizanlizumab was relatively well-tolerated during SUSTAIN's 52-week treatment phase, however risks for long-term adverse outcomes are hard to judge, a problem common to all newly introduced treatments with a new mechanism of action. The FDA is requiring several postmarketing studies, including a clinical trial to assess the risk of infusion-related reactions and immunogenicity, bleeding complications, and infections.

Overall, we judged that the statistically significant reduction in pain crises was enough to give adequate certainty that crizanlizumab will provide a positive net health benefit. However, the difficulty in estimating the amount of longer-term organ system benefit conveyed by the absolute reduction in acute pain crises, coupled with uncertainty about long-term safety, gives us only moderate certainty overall in the magnitude of net health benefit, which seems likely to range from small to substantial, a "B+" rating in the ICER Evidence Matrix.

Voxelotor versus Optimal Usual Care

Compared to optimal usual care alone, voxelotor improved laboratory parameters, including an increase in hemoglobin and reductions in hemolysis markers such as bilirubin and percent reticulocytes. But voxelotor did not significantly reduce the annualized incidence rate of acute pain crises and has not yet demonstrated an effect on quality of life. Annualized incidence rates of acute pain crises were very similar across the voxelotor arms and placebo arms, such that the best suggestion of a trend toward improvement might be an approximate risk reduction of 13% with a confidence interval that crosses one (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); a longer duration of follow-up will be necessary to determine whether voxelotor improves this important outcome. Although the rate of acute pain crises and quality of life were secondary outcomes, they are important outcomes to patients and linking an increase in hemoglobin levels to these or other patient-important outcomes will be helpful over time. We did not identify any data related to health care utilization for voxelotor that would indicate a reduction in transfusions. Although it seems logical to assume that for some patients there will be reductions in transfusions over time, the clinical trial reported more transfusions in the group who received voxelotor than in the placebo group.

Does an increase of 1 g/dL of hemoglobin improve short or long-term health outcomes? We heard from some clinical experts that even an additional 1 g/dL of hemoglobin can reduce patient fatigue and potentially reduce the risks for specific longer-term harms such as high-output congestive heart failure.

Separate from questions about increases in hemoglobin is the extent to which reduction in hemolysis improves short or long-term outcomes. Again, some clinical experts feel there are strong correlational data to support the benefits of reduced hemolysis. For example, several studies have shown higher rates of leg ulcers, priapism, renal dysfunction, stroke and mortality with higher rates of hemolysis and hemolytic byproducts, and there may be broader clinical implications as well.[39] But on the other side of this issue lies the uncertainty of whether there is a threshold of reduced hemolysis required to achieve clinical benefit, and the short-term data available make it impossible to determine the answer to this question.

Safety issues, including rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial. Further study of the long-term safety of voxelotor, however, is required.

Overall, we felt that it was difficult to ascertain the net health benefit of voxelotor with available data at its launch. Nonetheless, we feel that there is less than a 10% chance that treatment will lead to net harm over a broad population. Given that we cannot determine the magnitude of the clinical benefits but feel they are likely to be somewhat greater than usual care, we have assigned a rating of "Promising but Inconclusive" (P/I) to the comparative clinical effectiveness of voxelotor at this time.

L-Glutamine versus Optimal Usual Care

The Phase II and Phase III trials of L-glutamine showed reductions in the number of acute pain crises and hospitalizations, although these results were not robust to different analytic methods needed to account for a large and differential rate of trial withdrawal across treatment arms. This led the FDA to conclude that results trended in favor of L-glutamine but that the magnitude of benefit was uncertain.[38] L-glutamine is considered to have a relatively benign safety profile, with few SAEs in the Phase III trial determined to be related to therapy. Nevertheless, a trial that administered higher doses and different formulations of L-glutamine in critically ill patients (without SCD) with multiorgan failure found that L-glutamine increased mortality and the FDA could not categorically rule out that the deaths that occurred in the Phase II and III trials in patients with SCD were unrelated to the study drug. Overall, there were problems with the conduct and analyses of the available phase II and phase III trials that lead to uncertainty about the magnitude of clinical benefit as well as some *a priori* safety concerns from the use of L-glutamine in other clinical settings.

We therefore judged that the findings on clinical benefit are too uncertain to allow a clear determination of their magnitude, but it appears most likely that L-glutamine does provide some clinical benefit. However, with residual safety concerns and uncertainty about the clinical benefits due to trial limitations, we feel there remains a small risk that L-glutamine produces net harm overall, but that this risk is less than 10%. In our view, therefore, we rate the evidence on the comparative clinical effectiveness of L-glutamine to be "Promising but Inconclusive" (P/I) within the parameters of the ICER Evidence Matrix.

Long-Term Cost Effectiveness

The primary aim of this analysis was to estimate the lifetime cost effectiveness of treatments for SCD using a decision analytic model. Crizanlizumab, voxelotor, and L-glutamine, each combined with usual care, were compared to usual care alone. The model estimates outcomes that include life years gained, quality-adjusted life years (QALYs) gained, equal value life years gained (evLYG), acute and chronic clinical events, pain crises avoided, change in hemoglobin, and total costs for each intervention over a lifetime horizon. The base-case analysis used a health care sector perspective (i.e., direct medical care costs only), with the societal perspective as a co-base case.

The base-case model is meant to represent the patients for whom treatment is indicated and for whom there are efficacy data. To do so, the base-case model uses average patient characteristics from the trial, such as the average of the median ages reported in the trials (24 years), the proportion of females (52%), and a baseline rate of three acute pain crises per year.

Where possible, model inputs were informed by real world evidence from both published CMS national-level data and *de novo* evidence generation from a dataset of over 30,000 patients with SCD in the US with private insurance or Medicare. These data allowed us to estimate baseline rates

of acute and chronic conditions and the costs of these conditions. Model inputs for the societal effects of SCD were informed by a patient and caregiver survey conducted by Sick Cells that provided data from approximately 500 patients on how SCD affected patients' ability to work and attend school. Other model inputs were found in the published literature, including estimated effects of changes in hemoglobin and pain crises on acute and chronic conditions, and how conditions are associated with each other and with mortality. Data on the health-related quality-of-life of health states were also found in the literature.

Due to a lack of data for some model inputs, it was necessary to make a number of assumptions in constructing the cost-effectiveness model. In general, where there was uncertainty in the evidence, we made assumptions that tended to favor the treatments. Despite the lack of evidence from the clinical trials of treatment effects on quality-of-life we assumed that reducing pain crises and improving hemoglobin levels would lead to improved quality-of-life. At this time there is no data on the durability of the effects observed in the clinical trials, however, we assumed that the trial effects would be maintained through out the lifetime of the patient. We also assumed that treatment effects were similar regardless of the patient's genetic mutation, as treatment effects were not consistently available by genetic mutation. Actual treatment effects from the trials were representative of a mixed genotype population. It was also assumed that all discontinuation occurred within the first year of treatment. Treatments had relatively high discontinuation rates; assuming patients stayed on treatment after one year allowed us to model the effects and costs of lifetime treatment for some patients. We also assumed that drug-related treatment-emergent adverse events were treated with a physician visit. These were not modeled as having a significant effect on health-related quality-of-life as treatment-related adverse events reported in the trials were expected to be transitory and treatable with over-the-counter medication or a visit to the physician.

Estimated annual net costs of drugs were $96,354 for crizanlizumab, $92,584 for voxelotor and $30,046 for L-glutamine and were estimated at a 27% reduction from the list price (Table ES.1)

Table ES.1. Drug Cost Inputs

Drug	WAC per Package/Vial	Discount From WAC	Net Price Per Package/Vial	Net Price per Year§
Crizanlizumab (Adakveo®) **Infusion: 5.0 mg/kg, administered at weeks 0, 2, and then every 4 weeks**	$2,357/vial	27%	$1,721	$96,354
Voxelotor (Oxbryta®) **Oral: 1500 mg, once daily**	$10,417	27%	$7,604	$92,584
L-glutamine (Endari®)* **Powder, for oral solution: 5-15 grams, depending on body weight, twice daily**	$1,110/package	26%	$822.61†	$30,046

WAC: wholesale acquisition cost

*Price per package of 60 5g packets
†Federal Supply Schedule (FSS) price as of March 1, 2020
§1 year = 365.25 days or 52 weeks

Base-Case Results

Base-case results are reported from both a health care perspective and a societal perspective. The health care perspective includes only direct health care costs; the societal perspective also includes lost productivity costs to the patient, caregiver and out-of-pocket costs, and an effect on caregiver quality-of-life. The societal perspective includes assumptions optimistic for the treatments, including an assumption that caregivers experience a 10% disutility of that experienced by patients.

Health Care Sector Perspective

The base-case results show the lifetime costs for a patient on usual care from age 24 are approximately $1.2 million. The model estimates that usual care patients with a baseline risk of three acute pain crises per year are expected to experience 43 acute pain crises over their lifetime. Not all patients will have a myocardial infarction, AKI/renal infarction, or stroke; the model estimates a rate of 18 myocardial infarctions per 100 patients, 2 AKI/renal infarcts per 100, and 59 strokes per 100. Each treatment below is compared to the same usual care arm.

Treatment costs for crizanlizumab are approximately $970,000 over the lifetime, with cost-savings of approximately $98,000 from avoided acute and chronic conditions. Cost offsets are due to avoiding costs of acute and chronic conditions, which are lower for patients on crizanlizumab than with usual care alone. The model estimates that patients treated with crizanlizumab will experience 27 acute pain crises over their lifetime and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction and stroke. Incremental cost-effectiveness of crizanlizumab compared to usual care is estimated to be $432,000 per life year (LY) gained, $509,000 per evLYG and $1.1 million per QALY gained.

Treatment costs for voxelotor are approximately $1.1 million over the lifetime. The model estimates that patients treated with voxelotor will experience 42 acute pain crises over their lifetime, and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction, and stroke. Patients on voxelotor are predicted to experience an average increase in hemoglobin levels of 1.2 g/dL. Given the assumption that increases in hemoglobin with voxelotor produce benefits analogous to higher hemoglobin levels in other settings, this results in patients on voxelotor having the fewest stroke events over their lifetime, 37 per 100 patients. Incremental cost-effectiveness of voxelotor compared to usual care is estimated at approximately $550,000 per LY gained, $589,000 per evLYG, and $1.1 million per QALY gained. Note that these results rely on the inclusion of several assumptions that tended to favor the treatment. Despite a lack of information on a direct treatment effect of voxelotor on other outcomes of interest, we assumed that acute events and chronic conditions would be impacted by the reduction in number of acute pain crises, changes in

hemoglobin on risk for acute and chronic conditions including stroke, fatigue, chronic kidney disease, and pulmonary hypertension.

Treatment costs for L-glutamine are approximately $299,000 over the lifetime, with cost-savings of approximately $59,000 from avoided acute and chronic conditions. The model estimates that L-glutamine patients will experience an average of 34 acute pain crises over their lifetime and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction, and stroke. Incremental cost-effectiveness of L-glutamine compared to usual care is estimated to be approximately $238,000 per LY gained, $270,000 per evLYG, and $604,000 per QALY gained.

Table ES.2. Base-Case Results

Regimen	Cost	QALYs	Life Years	evLYG
Usual Care	$1,174,000	8.07	14.34	8.07
Crizanlizumab	$2,046,000	8.87	16.36	9.78
Voxelotor	$2,291,000	9.10	16.37	9.96
L-glutamine	$1,414,000	8.47	15.35	8.96

QALY: quality-adjusted life year, evLYG: equal value life-years gained

Table ES.3. Pairwise Results for Crizanlizumab, Voxelotor and L-Glutamine Compared to Usual Care Alone

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	Incr. evLYG	Incremental cost-effectiveness ratio (per QALY)	Incremental cost-effectiveness ratio (per LYs)	Incremental cost-effectiveness ratio (per evLYG)
Crizanlizumab	$872,000	0.80	2.02	1.71	$1,086,000	$432,000	$509,000
Voxelotor	$1,117,000	1.03	2.03	1.90	$1,082,000	$550,000	$589,000
L-glutamine	$240,000	0.40	1.01	0.89	$604,000	$238,000	$270,000

Incr.: incremental, LY: life year, QALY: quality-adjusted life year, evLYG: equal value life-years gained

Societal Perspective

The societal perspective affects the total costs and the QALYs in each analysis. The economic value of lifetime productivity gains from treatment compared to usual care alone ranged from approximately $129,000 for L-glutamine to $155,000 for crizanlizumab and voxelotor. Crizanlizumab had the highest out-of-pocket costs avoided, caregiver burden avoided, and improvement in school attendance, as these outcomes were closely related to acute events. Voxelotor had the most improvement in caregiver QALYs, as these were more directly related to chronic health states. We calculated the incremental cost-effectiveness ratios from a societal perspective by subtracting the productivity gained, the out-of-pocket costs avoided, and the

caregiver burden avoided from the total cost differences and adding the caregiver QALYs to the patient QALYs. The cost per QALY of L-glutamine was affected the most, as the productivity gained was substantial compared to the total cost of the treatment.

Table ES.4. Results for the Base Case for Crizanlizumab, Voxelotor, and L-glutamine versus Usual Care Alone: Modified Societal Perspective

Treatment	Crizanlizumab	Voxelotor	L-glutamine
Productivity Gained	$155,300	$155,600	$129,000
Out-of-Pocket Costs Avoided	$2,400	$40	$1,400
School Attendance (sick days avoided)*	112	40	66
Caregiver Burden Avoided	$16,200	$1,800	$9,400
Caregiver QALYs	0.05	0.08	0.03
Cost per LY gained	$364,000	$474,000	$121,000
Cost per evLYG	$416,000	$488,000	$134,000
Cost per QALY	$859,000	$866,000	$289,000

*To capture an effect on school attendance the costs and outcomes were estimated for a population being treated from 5 years old. LY: life year, QALY: quality-adjusted life year, evLYG: equal value life-years gained

Sensitivity Analyses

Sensitivity analyses demonstrate that, for all three treatments, the cost of the treatments, the utility of uncomplicated sickle cell disease, and the treatment effect on acute pain crises are the major drivers of cost per QALY, for both the health care and modified societal perspectives. The effect of treatment on hemoglobin level and the impact of hemoglobin level on stroke and CKD also had relatively large impacts on the estimated cost per QALY of voxelotor. For the societal perspective, the degree of work impairment was also an important driver, especially for L-glutamine. Overall, the estimated cost per QALY did not fall below $500,000 for crizanlizumab or voxelotor in any of the sensitivity analyses. However, the cost per QALY ratio for L-glutamine fell below $150,000 per QALY using the societal perspective, if assumed to have higher effectiveness or lower cost, or greater impact on work impairment.

Uncertainty in the model estimations was explored using probabilistic sensitivity analysis. The probabilistic outputs are very similar to the deterministic outputs. The credible intervals demonstrate some large variations in the total costs, pain crises, life-years gained, evLYG and QALYs from the parameter uncertainty. However, the cost-effectiveness acceptability curves showed that the probability that any of the treatments are cost-effective at generally accepted thresholds is essentially zero. At a threshold of $1,000,000 per QALY the probability of cost-effectiveness is 0.40 for crizanlizumab, 0.97 for L-glutamine and 0.27 for voxelotor.

Scenario Analyses

Analysis of a population with 10 acute pain crises per year results in a larger difference in acute pain crises avoided and lower incremental cost-effectiveness ratios for all treatments. To reduce the incremental cost-effectiveness ratio to $150,000 per QALY, the baseline acute pain crisis rate would

have to be 20 per year for crizanlizumab and 9.4 per year for L-glutamine, while there was no number of acute pain crises that would reduce the cost per QALY to $150,000 for voxelotor. From the societal perspective in a population with 10 acute pain crises per year, L-glutamine dominates usual care, meaning that it is less expensive, has higher LY gained, higher evLYG and higher QALYs.

Analyses of younger populations, starting treatment at 16 years old with crizanlizumab, 12 years old with voxelotor, and 5 years old with L-glutamine, resulted in a slightly higher cost per QALY for crizanlizumab and voxelotor and a lower cost per QALY for L-glutamine. This is likely due to the lower baseline risk of acute events and chronic conditions in the younger population. This results in improvements in acute pain crises having less of an impact on acute events and chronic conditions at these younger ages.

Threshold Analyses

The threshold analyses calculate the drug price at which each treatment would be cost-effective at different relevant thresholds, with results for the health care sector perspective shown in Table ES.5. For crizanlizumab to be cost-effective at $50,000 per QALY, the price would have to be $230 per vial or approximately $12,870 annually, and approximately $20,920 annually at $150,000 per QALY. For voxelotor to be cost-effective at $50,000 per QALY, the price would have to be $332 per package or approximately $4,050 annually, and $12,630 annually at $150,000 per QALY. L-glutamine would be cost-effective at 50,000 per QALY at $217 per package or approximately $7,910 annually, and at $11,910 annually at $150,000 per QALY.

Table ES.5. Annual Drug Costs at List and Discount Prices and at Prices at Which Each Treatment is Cost-effective at Specific Thresholds: Health Care Perspective[40]

Treatments	Thresholds of Interest						
	Assumed Net Price	$50K per QALY	$100K per QALY	$150K per QALY	$50K per evLYG	$100K per evLYG	$150K per evLYG
Crizanlizumab	$96,350	$12,870	$16,890	$20,920	$17,430	$26,030	$34,620
Voxelotor	$92,580	$4,050	$8,340	$12,630	$7,630	$15,510	$23,380
L-glutamine	$30,050	$7,910	$9,910	$11,910	$10,380	$14,850	$19,330

evLYG: equal value life years gained, QALY: quality-adjusted life year

Using the societal perspective analysis (Table ES.6), crizanlizumab was cost-effective at $50,000 per QALY at a price of $30,580 annually, and $39,170 annually at $150,000 per QALY. Voxelotor was cost-effective at thresholds of $50,000 and $150,000 per QALY at prices of $17,460 and $26,710 annually, respectively. L-glutamine was cost-effective at thresholds of $50,000 and $150,000 per QALY at prices of $22,060 and $26,320 annually, respectively.

Table ES.6. Annual Drug Costs at List and Discount Prices and at Prices at Which Each Treatment is Cost-effective at Specific Thresholds: Modified Societal Perspective [40]

Treatments	Input Prices		Thresholds of Interest					
	List Price	Assumed Net Price	$50K per QALY	$100K per QALY	$150K per QALY	$50K per evLYG	$100K per evLYG	$150K per evLYG
Crizanlizumab	$132,000	$96,350	$30,580	$34,870	$39,170	$34,880	$43,470	$52,070
Voxelotor	$127,000	$92,580	$17,460	$22,090	$26,710	$20,720	$28,590	$36,470
L-glutamine	$40,540	$30,050	$22,060	$24,190	$26,320	$24,400	$28,870	$33,350

evLYG: equal value life years gained, QALY: quality-adjusted life year

Model Validation

Comparison of the prevalence of pulmonary hypertension, heart failure, and chronic kidney disease as reported by CMS[40] and as estimated in the model suggests that the predicted prevalence in the model is very similar to that of the Medicare population in terms of chronic disease prevalence. In addition, model validation demonstrates that the usual care population in the model has a life-expectancy similar to that reported in the literature for people with SCD.

Summary and Comment

As discussed above, the model made a number of assumptions favorable to all the medications, but particularly to voxelotor given the lack of evidence that voxelotor actually reduces events or the need for transfusion. In the case of L-glutamine, we had concerns about the validity of the results from the clinical trials given differential dropout rates. The report concluded above that the evidence for net benefit was less conclusive for L-glutamine and voxelotor than for crizanlizumab, and that should be kept in mind when interpreting the results discussed below, which use point estimates of benefit that have more or less uncertainty for the various therapies.

Treatment costs were the main driver of the cost-effectiveness results, with average annual costs (after accounting for discontinuation) of approximately $79,000 for crizanlizumab, $78,000 for voxelotor and $24,000 for L-glutamine using net prices. Combined with relatively small improvements in QALYs gained, incremental cost-effectiveness ratios ranged from $604,000 to $1.1 million per QALY using a health care sector perspective. Using a societal perspective including productivity gains and other indirect costs, incremental ratios were lower but still above $150,000 per QALY, ranging from $289,000 for L-glutamine to $866,000 per QALY for voxelotor. None of the scenario analyses undertaken lowered the estimated cost per QALY of crizanlizumab or voxelotor to less than $150,000 per QALY from a health care sector or societal perspective, although scenario analyses suggest treatment is most cost-effective for patients with higher rates of acute pain crises. Patients who experience 10 acute pain crises per year may have a cost per QALY as low as $144,000 with L-glutamine.

Although a reduction in acute pain crises and increase in hemoglobin will provide relief to patients, they will continue to suffer from other acute and chronic conditions that will have a significant impact on their quality of life. The impact of these therapies on these other acute and chronic conditions has yet to be demonstrated in clinical trials, although we made favorable assumptions that included impacts of these treatments on several of these conditions. As a result, there is currently a large difference in the cost per QALY and the cost per life-year and evLYG. For example, from the health care perspective, cost per evLYG ranged from approximately $270,000 for L-glutamine to $589,000 for voxelotor, and from $134,000 per evLYG for L-glutamine to $488,000 per evLYG for voxelotor. Patients who experience 10 acute pain crises per year may have a cost per evLYG below $150,000 with crizanlizumab or L-glutamine. Using a societal perspective including productivity gains and other indirect costs, incremental ratios were lower but still above $150,000 per QALY in almost all cases.

Disparities

It is important to note that economic models such as this one cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations such as patients with SCD. It is also unclear what impact treatments for these populations will have on those systemic issues, or vice versa. For example, the majority of people with SCD in the US have African American heritage. Life expectancy at birth is 4.442% lower for blacks than for whites in the US (75.3 years vs. 78.8 years).[41] In an exploratory analysis, we estimated that if all people with SCD were treated with crizanlizumab and all were assumed to be African-American, the increase in life years would decrease the overall disparity in life expectancy by a relative 3.6% (i.e., to 4.426% lower rather than 4.442%).

As an example of these systemic issues, we compared the life expectancy of patients with SCD in our model to the life expectancy of a matched non-SCD population and to the general US population (Figure ES.1). The estimate of life expectancy for the matched non-SCD cohort was obtained from an analysis by Lubeck et al.[42], which developed a non-SCD population cohort that matched the age, sex, and race/ethnicity of the SCD population. Lubeck et al. reported a similar 3-year difference in life expectancy between the US population and the matched non-SCD cohort as seen above. Treatment with crizanlizumab or voxelotor was estimated in the model to add approximately 4 years (undiscounted) to life expectancy for treated SCD patients, reducing the disparity from 45% to 40% compared to the general population. Treatment with L-glutamine was estimated to add approximately 1.9 undiscounted years to life expectancy for treated SCD patients, reducing the disparity to 42.5% compared to the general population.

Figure ES.1. Comparison of Life Expectancy for People with Sickle Cell Disease (with and without Treatment) to Matched Non-Sickle Cell Disease and General US Populations

LE: life expectancy, SCD: sickle cell disease

Given the severe impact of this condition on people with sickle cell disease, on top of the racial disparities in health care faced by most of these patients, decision-makers in the US may wish to consider giving special weighting to other benefits and to contextual considerations that would lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES.6. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	N/A
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	Effective treatment could potentially reduce the gap in life expectancy between black and white Americans and between the poor and rich in the US. Further, if these new therapies can be shown to directly impact other acute and chronic morbidities outside of those measured in the current clinical trials, patients could experience significant improvements in their quality of life.
This intervention will significantly reduce caregiver or broader family burden.	Crizanlizumab has demonstrated the greatest likelihood of reducing disease burden due to acute pain crises while voxelotor and L-glutamine may be able to provide more convincing evidence in the future.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	All three therapies offer novel mechanisms of action both from the existing therapies and from each other.
This intervention will have a significant impact on improving return to work and/or overall productivity.	If a decrease in the number of pain crises and increase in hemoglobin level translate into a measurable improvement in quality of life, there is the potential for all three therapies to improve both patient and caregivers' ability to return to school and/or work and improve overall productivity. However the impact on return to work or productivity will be determined by the magnitude of impact on patients.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	The therapies may bring new hope to patients who had previously given up on trying to feel better and it may encourage more patients to see their doctors in order to access these new therapies. All three therapies have different mechanisms of action and at some future time may be used in combination with other established treatments or with each other in order to further improve patient outcomes and quality of life.

Contextual Considerations

Table ES.7. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	All three therapies treat SCD which has an extremely high burden on both quality of life and length of life. This burden also extends to family members and caregivers because of its severity.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Patients with SCD are born with the condition, experience their first symptoms before their first year of life and have significant morbidity and mortality even at a young age.
This intervention is the first to offer any improvement for patients with this condition.	N/A
Compared to usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	We do not have long term safety data for any of these new therapies.
Compared to usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	We do not know the durability of effect over the long term for any of these new therapies.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	These therapies have the potential to bring new enthusiasm for both patients and physicians which may bring solutions to an historically broken, dysfunctional and dispassionate healthcare system thereby further reducing the psychological and emotional toll of SCD.

Health Benefit Price Benchmarks

Health Care Perspective

Annual health benefit price benchmarks (HBPBs) of crizanlizumab, voxelotor, and L-glutamine are presented in Table ES.7. The health benefit benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY (or evLYG) gained. For crizanlizumab, price discounts of approximately 84% to 87% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For voxelotor, prices approximately 90% to 93% below WAC would achieve $100,000 to $150,000 per QALY threshold prices. For L-glutamine, prices approximately 71% to 76% below WAC would achieve $100,000 to $150,000 per QALY threshold prices.

Table ES.7. Annual Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
Per QALY Gained	$132,000	$16,890	$20,920	84% to 87%
Per evLYG		$26,030	$34,620	74% to 80%
Voxelotor				
Per QALY Gained	$127,000	$8,340	$12,630	90% to 93%
Per evLYG		$15,510	$23,380	82% to 88%
L-glutamine				
Per QALY Gained	$40,540	$9,910	$11,910	71% to 76%
Per evLYG		$14,850	$19,330	52% to 63%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

The annual price at which crizanlizumab meets the $100,000 to $150,000 per evLYG range for use in these patients would require a 74% to 80% discount. For voxelotor, the relevant cost per evLYG price range would require 82% to 88% discounts for the $100,000 to $150,000 per evLYG thresholds. For L-glutamine, the relevant cost per evLYG price range requires 52% to 63% discounts to reach the $100,000 to $150,000 per evLYG thresholds. The cost per evLYG price ranges are higher than the cost per QALY range for all three of these drugs because each of these treatments is estimated to result in higher evLYG than QALYs gained, reflecting the low quality of life for many patients with sickle cell disease during later years and the potential for these treatments to increase the life expectancy of patients with sickle cell disease.

Modified Societal Perspective

Annual health benefit price benchmarks (HBPBs) of crizanlizumab, voxelotor, and L-glutamine using the modified societal perspective are presented in Table ES.8. For crizanlizumab, price discounts of approximately 70% to 74% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For voxelotor, prices approximately 79% to 83% below WAC would achieve $100,000 to $150,000 per QALY threshold prices. For L-glutamine, prices approximately 35% to 40% below WAC would achieve $100,000 to $150,000 per QALY threshold prices.

Table ES.8. Annual Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine: Modified Societal Perspective

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
Per QALY Gained	$132,000	$34,870	$39,170	70% to 74%
Per evLYG		$43,470	$52,070	61% to 67%
Voxelotor				
Per QALY Gained	$127,000	$22,100	$26,710	79% to 83%
Per evLYG		$28,590	$36,470	71% to 77%
L-glutamine				
Per QALY Gained	$40,540	$24,190	$26,320	35% to 40%
Per evLYG		$28,870	$33,350	18% to 29%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

The annual price at which crizanlizumab meets the $100,000 to $150,000 per evLYG range for use in these patients would require a 61% to 67% discount. For voxelotor, the relevant cost per evLYG price range would require 71% to 77% discounts for the $100,000 to $150,000 per evLYG thresholds. For L-glutamine, the relevant cost per evLYG price range requires only 18% to 29% discounts to reach the $100,000 to $150,000 per evLYG thresholds. As was seen with the health care perspective results, the cost per evLYG price ranges are higher than the cost per QALY range for all three of these drugs when using the societal perspective. This is because, in conditions such as sickle cell disease where treatments may extend lifespan at lower utility, the evLYG from these treatments is greater than the estimated QALYs gained from treatment, leading to lower incremental cost-effectiveness ratios and higher threshold prices.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of each recently approved drug (crizanlizumab and voxelotor) for prevalent individuals in the United States (US) with SCD. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. Following the FDA label indications, we restricted the prevalent SCD population to adults and pediatric patients aged 16 years and older for crizanlizumab (approximately 87,500, or 17,500 patients each year over five years) and to adults and pediatric patients aged 12 years and older for voxelotor (approximately 93,000, or 18,600 patients each year over five years). In our estimates of

potential budget impact, we used the wholesale acquisition costs (WAC), assumed net prices, and the $50,000, $100,000, and $150,000 cost-effectiveness threshold prices for each drug, and the five-year annualized potential budget impact threshold of $819 million per year for new drugs.

In the population eligible for crizanlizumab, approximately 21% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at crizanlizumab's WAC. Approximately 31% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. All eligible patients could be treated at the $150,000, $100,000 and $50,000 threshold prices, with estimated potential budget impact of approximately 8% of the threshold at the $150,000 threshold price and cost savings at the $100,000 and $50,000 threshold prices.

Approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at voxelotor's list price (WAC). Approximately 23% of eligible patients could be treated without crossing the budget impact threshold at the assumed net price. All eligible patients could be treated at the $150,000, $100,000 and $50,000 threshold prices, with estimated potential budget impact of approximately 24% of the threshold at the $150,000 threshold price, 2% of the threshold at the $100,000 threshold price, and cost savings at the $50,000 threshold price.

The potential budget impact analysis showed cost-savings in the first five years for crizanlizumab at the $100,000 and $50,000 per QALY threshold prices and for voxelotor at the $50,000 per QALY threshold prices. The prices at different cost-effectiveness thresholds are calculated over the lifetime of the model, while the potential budget impact analysis focuses on the first five years of treatment. In this case, most cost offsets occur early on, as treatment delays development of chronic conditions relative to usual care. Therefore, at the threshold prices, potential budget impact could be cost saving in the short term. As patients eventually develop more chronic conditions, the remaining impact of treatment is mainly on acute events; this leads to decreases in cost offsets while the treatment cost remains relatively constant, resulting in higher (positive) net costs in later years.

1. Introduction

1.1 Background

Sickle cell disease (SCD) is a broad term referring to a group of inherited disorders carried by the beta (β) allele of the hemoglobin (Hb) gene. It is characterized by abnormal hemoglobin polymerization during deoxygenation resulting in sickle-shaped erythrocytes (red blood cells [RBCs]). SCD includes the genotypes HbSS, as well as the compound heterozygous genotypes HbSβ^0 thalassemia, HbSC, HbSD, and HbSβ$^+$ thalassemia.[8] The genotypes HbSS and HbSβ^0 thalassemia have similar clinical characteristics and together are frequently referred to as sickle cell anemia. Conversely, the heterozygous state with one normal gene and one Hb S gene (HbAS) is the carrier state and is referred to as "sickle cell trait". Sickle cell trait usually does not have clinical manifestations and confers protection against plasmodium falciparum malaria.[43]

Clinical manifestations of SCD derive from at least three different pathophysiologic mechanisms: the loss of deformability of the RBC leading to vascular obstruction and ischemia; a shortened lifespan of the RBC leading to both intravascular and extravascular hemolysis; a sticky RBC surface increasing adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions.[3]

Rates of SCD and sickle cell trait vary considerably by geography with the highest rates found in populations arising from areas where, historically, resistance to plasmodium falciparum malaria conferred a survival advantage.[43] These include equatorial Africa, Brazil, Saudi Arabia and central India. The incidence of SCD is estimated at 300,000 to 400,000 live births globally per year. In the United States (US), the current best prevalence estimate is approximately 100,000 individuals with SCD, although comprehensive surveillance and reporting is lacking and the exact number of cases in the US is unknown.[2]

A marked decrease in mortality in infancy occurred in the US from 1979-2006, presumably due to the implementation of universal newborn screening, penicillin prophylaxis, and the use of conjugated pneumococcal vaccine.[2] During that same time, peak mortality shifted from the middle third decade of life to the late fourth decade of life with the mean age of death being 39 years.[44] Despite improved survival, life expectancy continues to be 20-30 years less than the US general population.[2]

Recurrent acute pain crisis, or vaso-occlusive crisis (VOC), is one of the most prevalent manifestation of SCD. An understanding of the pathophysiology of acute pain crises continues to evolve with recent models focused on the complex cascade of inflammation, adherence of leukocytes, and blood flow obstruction. The management of acute pain crises is extremely

important in patients with SCD yet is often misunderstood or inadequately addressed across all health care settings.[8]

In addition to acute pain crises, patients experience significant acute and chronic morbidity over time. Acute complications include serious infections such as meningitis, osteomyelitis, and sepsis, and non-infectious complications such as stroke, renal necrosis, and priapism.[4] Acute chest syndrome (ACS) is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms; some episodes of ACS are triggered by infection.[45] Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality.[4] Individuals with SCD face ongoing and evolving lifelong difficulties as a result of their disease. As their bodies grow, develop, and age, new problems can emerge while intermittent and persistent vaso-occlusion/ischemia produce an accumulation of injuries over time.[43] Resultant health care costs are high, with the total health system economic burden of SCD estimated at $2.98 billion per year in the US with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[5]

Our understanding of the relationship of hemoglobin levels and ongoing hemolysis, to acute and chronic morbidity and survival continues to evolve. Low hemoglobin levels have been associated with fatigue, silent cerebral infarct, pulmonary hypertension, kidney disease, and mortality.[46-49]. More recently, the clinical manifestations and risk of mortality have been linked to the degree of intravascular hemolysis and the release of lysed erythrocyte byproducts.[39,50] In fact some of the heterogeneity in the phenotypic expression of SCD is now being attributed to subphenotypes with some patients expressing more hemolytic anemia related manifestations of the disease and others more vaso-occlusive morbidities. The interrelationship of anemia related morbidity and VOC related morbidity remains unclear. Nonetheless, future individualized care plans will undoubtedly incorporate this level of specificity as new information continues to emerge.

The impact of SCD on quality of life (QOL) is complex and affects both patients and their caregivers in many ways. In addition to the health-related burden of disease, many other factors further diminish QOL. The lack of treatment options, discrimination, stigma around the need for chronic pain management, disruption of family and social activities, missed school and/or work all combine to make living with SCD very difficult.[51,52] Children worry about dying early from the disease. Pain and fatigue limits their ability to perform well in school and maintain relationships with friends. They feel the impact of chronic pain, daily fatigue, and emotional distress, and often recognize that they are not able to live a normal life like their friends. As adult patients they often carry the same concerns as in childhood with the addition of mobility issues, difficulty managing work and careers, difficulty caring for themselves and their families, and ongoing concerns about the progression of their disease.[6] SSCD is a lifelong, all-encompassing, biopsychosocial condition, that constitutes one of the most difficult of all chronic illnesses for patients and their families.[6]

Treatment for SCD

We heard from patients and clinicians that the picture of "baseline" or "usual" care for patients with SCD is highly variable. Deep dysfunction in care is driven by poor coordination within provider systems and by barriers to access that arise from a broad range of factors including systemic racism, uninformed clinicians, poverty, and insurance systems poorly designed to coordinate coverage for patients with multi-system chronic conditions. Upon that background of poor performance in service of patients with SCD, innovation in specific disease-modifying treatments has also been lacking for several decades. Until recently only three specific interventions were considered helpful for SCD: stem cell transplantation, chronic transfusion with packed RBCs, and hydroxyurea.[7] While stem cell transplant engraftment rate is dependent upon the degree of myeloablation, it can result in the complete replacement of abnormal hemoglobin with completely normalized hemoglobin and resolve hemolysis. Unfortunately, the degree of myeloablation required and the availability of matched donors limit its use. Chronic transfusion is generally used for primary or secondary stroke prevention; hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises, and in those with a history of ACS or severe anemia.[8] Acute pain crisis may be managed with pain medications including opioids, and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments.[8]

Within the past several years several new options have gained regulatory approval in the US (Table 1.1). L-glutamine (Emmaus) is a precursor of nucleic acids and nucleotides that play a key role in the regulation and prevention of oxidative damage to red blood cells. [9]It was approved by the US Food and Drug Administration (FDA) on July 7, 2017 to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older. It is a powder to be mixed with liquid or food and is administered orally twice daily. Crizanlizumab (Novartis AG), is a humanized monoclonal antibody that binds to P-selectin. P-selectin is expressed on the surface of endothelial cells and platelets and it is thought that blockage could reduce the static adhesion of sickled RBCs thus reducing the vaso-occlusion and inflammation.[10] It was approved by the FDA on November 15, 2019 to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD. It is administered intravenously in two loading doses two weeks apart and then every four weeks thereafter. Voxelotor (Global Blood Therapeutics, Inc.) is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissociation curve.[11] Voxelotor was approved by the FDA on November 25, 2019 for the treatment of SCD in adults and pediatric patients 12 years of age and older. It is a tablet administered orally once a day with or without food.

Table 1.1. Recently Approved Therapies for SCD

	Date of FDA Approval	FDA Indication	FDA Dosage	WAC	Cost per Year*
Crizanlizumab (Adakveo®)	11/15/2019	Indicated to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD	Administer 5 mg/kg (IV) over a period of 30 minutes on week 0, week 2, and every 4 weeks thereafter	$2,357.14 per 10ml vial	$96,354
Voxelotor (Oxbryta™)	11/25/2019	Indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older.	Administer 1,500 mg tablet orally once daily with or without food	$10,417.00 per package of 90 500mg pills	$92,584
Pharmaceutical grade L-Glutamine (Endari®)	7/7/2017	Indicated to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older	Administer 5 – 15 grams orally, based on body weight, twice daily. Mix powder with food or liquid.	$1,110 per package of 60 5g packets	$30,046

IV: intravenous, SCD: sickle cell disease, WAC: wholesale acquisition cost

WAC per Redbook® accessed on December 17, 2019

*Based on a 27% discount off WAC for crizanlizumab and voxelotor; L-glutamine cost represents Federal Supply Schedule (FSS) price as of March 1, 2020

1.2 Scope of the Assessment

Two new therapies and one relatively new therapy have become available for patients with SCD. Questions on the impact of these therapies on both acute and chronic complications of SCD along with long term safety remain. Further, the alignment of costs with potential patient benefits for these new therapies is unclear. This assessment evaluates the clinical effectiveness and cost effectiveness of crizanlizumab, voxelotor, and pharmaceutical-grade L-glutamine for patients with SCD.

The scope for this assessment is described on the following pages using the Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) framework. Evidence was abstracted from randomized controlled trials (RCTs) and nonrandomized studies as well as high quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon adverse events (AEs). Our evidence review includes input from patients and patient advocacy organizations, including a survey of patients and caregivers,

data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessmentframework/grey-literature-policy/).

All relevant evidence was summarized qualitatively. We sought head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis were provided in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for SCD is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Crizanlizumab, L-Glutamine, and Voxelotor for SCD

Interventions
- Crizanlizumab + optimal usual care
- Voxelotor + optimal usual care
- L-Glutamine + optimal usual care

Comparators
- Optimal usual care alone

Population
Patients two years of age and older with sickle cell disease

Intermediate outcomes
- Laboratory measures

Key measures of benefit[*]
Acute
- Acute pain crisis
- Acute chest syndrome
- SCD-related hospitalization
- Need for acute blood transfusion

Chronic
- Chronic pain
- Health-related quality of life
- Other patient-reported outcomes

Mortality

Adverse events
- Death due to AEs
- Discontinuation due to AEs
- SAEs
- TEAEs

*Full list of outcomes of interest available in Appendix D
SCD: Sickle cell disease
SAE: Serious adverse event
TEAE: Treatment-emergent adverse event

AEs: adverse events, SAE: serious adverse event, SCD: sickle cell disease , TEAE: treatment emergent adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., laboratory measures), and those within

the square boxes are key measures of benefit (e.g., acute pain crisis). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the AEs of an action (typically treatment), which are listed within the blue ellipse.

Populations

The population of focus for this review is children and adults, two years of age and older, who have been diagnosed with SCD. Where data were available, we examined evidence for key subgroups suggested by clinical experts, including the following:

- Age
- Hydroxyurea use
- Use of chronic transfusions
- Sickle cell genotype
- Frequency of acute pain crises

Interventions

The interventions of interest for this review are listed below:

- Crizanlizumab (Adakveo®; Novartis AG) in addition to optimal usual care (e.g., hydroxyurea, transfusions)
- Voxelotor (Oxbryta™; Global Blood Therapeutics, Inc.) in addition to optimal usual care (e.g., hydroxyurea, transfusions)
- Prescription-grade formulations of L-Glutamine (e.g., Endari®; Emmaus Medical, Inc.) in addition to optimal usual care (e.g., hydroxyurea, transfusions)

Comparators

Evidence was sought to compare each intervention to "optimal usual care" as estimated by the placebo arm of the clinical trials. For context, we heard from both patients and clinicians that the documented care patients received in the "usual care" arm of the clinical trials was significantly better that what the average patient with SCD receives in the real world. Therefore, in our clinical review we chose to label the care patients received in the clinical trials as "optimal usual care". We are not seeking to compare the clinical effectiveness of the three new interventions directly to each other given differences in patient populations and outcome measures, but we will create a common population for economic modeling in order to provide all stakeholders with the ability to compare long-term cost-effectiveness.

Outcomes

This review examines key measures of benefit and safety associated with SCD, including, but not limited to, the outcomes listed below. Additional outcomes of interest, including intermediate and surrogate endpoints, are listed in Appendix D and were captured when evidence on such outcomes was identified.

Acute Outcomes

- Acute pain crisis
- Acute chest syndrome
- Acute myocardial infarction (MI)
- Stroke
- Acute kidney injury/Renal infarction
- Iron overload
- Splenic sequestration
- Priapism
- Change in hemoglobin
- Need for blood transfusion
- Quality of Life
- Hospitalization
- Mortality
- Change in hemolysis markers

Chronic Outcomes

- Pulmonary hypertension
- Heart failure
- Opioid tolerance/dependence
- Nephropathy/CKD
- Chronic chelation therapy
- Chronic pain
- Fatigue
- Other organ damage
- Neurocognitive dysfunction
- Mental health effects (e.g., depression, anxiety)
- Mortality

<u>Safety</u>

- Serious adverse events (SAE)
- AEs leading to discontinuation
- Treatment-emergent adverse events (TEAE)

Timing

Evidence on intervention effectiveness and evidence on harms was derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

1.3 Definitions

Acute Chest Syndrome (ACS)[53]: defined as a new radiodensity on chest radiography accompanied by fever and/or respiratory symptoms. ACS in adults with SCD requires prompt management to prevent clinical deterioration.

Acute Hepatic Sequestration[54]: patients with hepatic sequestration usually present with right upper quadrant pain, rapidly increasing hepatomegaly, and a falling hematocrit. Treatment of hepatic sequestration crisis involves prompt, aggressive restoration of blood volume. Typically, simple transfusion therapy is sufficient because the goal is to increase the hemoglobin to a level where the patient no longer has evidence of symptomatic anemia.

Acute Kidney Injury/Renal Infarction[55]: a condition resulting from a sudden disruption of blood flow to the renal artery. This may cause irreversible damage to kidney tissues.

Acute Splenic Sequestration[56]: a pooling of sickled red blood cells trapped in the spleen. This can cause the spleen to become enlarged, damaged, and not function properly. Splenic sequestration occurs more commonly in children and may cause sudden and severe anemia.

Chronic Kidney Disease (Nephropathy): defined in trials as either having a glomerular filtration rate (GFR) of less than 60ml/min/1.73 m^2 for greater than or equal to 3 months with or without kidney damage or having evidence of kidney damage for greater than or equal to 3 months, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage independent of cause.

Chronic Sickle Cell Pain: pain that does not resolve and lasts for more than 3 months.

HbSβ⁰ thalassemia[57]: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene that results in no production of HbA**.**

HbSβ⁺ thalassemia[57]: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

HbSC: sickle cell hemoglobin C disease

HbSD, HbSE and HbSO[57]: one inherited sickle cell gene ("S") and one gene from an abnormal type of hemoglobin ("D","E" or "O").

HbSS: homozygous sickle cell disease.

Opioid Tolerance[58]: occurs when a person using opioids begins to experience a reduced response to medication, requiring more opioids to experience the same effect.

Opioid Dependence[58]: occurs when the body adjusts its normal functioning around regular opioid use. Unpleasant physical symptoms occur when medication is stopped.

Pulmonary Arterial Hypertension (PAH)[59]: an elevation of pulmonary arterial systolic pressure (PASP) (greater than 20 mmHg at rest or greater than 30 mmHg with exercise) determined by right heart catheterization.

Vaso-occlusive Crisis (VOC): pain as a result of decreased blood flow in the microcapillaries (can include blood vessel blockage) resulting in tissue ischemia, occurring most commonly in bone or bone marrow. VOC's are also known as vaso-occlusive episodes or acute pain crises.

1.4 Potential Cost-Saving Measures in Sickle Cell Disease

ICER includes in its reports information on wasteful or lower-value services in the disease area of focus that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These are services that would not be directly affected by therapies for SCD (e.g., reduction in hospitalizations for acute pain crises), as these services were captured in the economic model. Rather, we sought services used in the current management of SCD beyond the potential offsets that arise from a new intervention. ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. We did not receive any suggestions related to SCD.

2. Patient Perspectives

"SCD is long overdue for a treatment and cure. It is buried in years of racial discrimination and to this day health care professionals treat based on assumptions not science. We need new drugs and treatments. [It's] about time we matter." – Parent of an individual living with SCD

An All-Encompassing Condition

Patients, family members, clinicians, and other members of the sickle cell community conveyed that it is hard to imagine a condition that ravages people's lives more than SCD. It is a danger to minimize the impact of the condition by reducing it to pain crises, or even to the better known acute and chronic organ effects. Pain crises are, of course, horrible to experience, and their accumulated impact over many years has effects on physical and mental health as well as the potential risks associated with opioid treatment.[12] In addition, the range of acute adverse effects of the condition includes almost every organ system, with strokes, ACS, and other life-threatening events a constant threat. These acute effects contribute to long-term risks for additional major organ dysfunction such as congestive heart failure and liver failure.[13]

But while these acute and long-term clinical harms are legion, patients and others emphasize that there is truly an all-encompassing biopsychosocial impact of SCD that is hard to capture, even by adding up one by one the multitude of organ system effects. There is fatigue, there is anxiety and depression, there is a hopelessness that has haunted patients with SCD. The condition presents challenges at home, school, work, and social relationships.[14] People with SCD often end up on formal disability programs, which unfortunately carries its own stigma. The cumulative effect of all these effects can be staggering.

"SCD is extremely unpredictable, even for the most aware patient. There is such a stigma that I feel from having this disease, wanting to do so much and contributing to society and yet I am limited from achieving many of my hopes and dreams." – Patient living with SCD

This is not to say that people with SCD are unable to function at a high level in society, but that the challenges and the barriers are extraordinary. One of the most important perspectives we learned from the SCD patient community and clinicians was that SCD remains a misunderstood, marginalized, condition. To fully appreciate the potential benefits of new treatments, a broad appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments.

Stigma and Limitations on Daily Life

Patients with SCD may appear healthy. An outward appearance of wellbeing can present additional barriers to appropriate care and contribute to social stigmas surrounding the disease. A general lack of awareness about the disease among nurses, hospitalists, and society at large means that healthy-looking patients suffering from an

> *"Day to day is hard. [We] are in pain a lot and our energy levels are low. We just want to be treated like the next. We are not lazy, we want fairness."*
> *– Patient living with SCD*

acute pain crisis, ACS, or other SCD-related complication may not be taken seriously. Patients presenting at the ER may be made to wait longer before receiving attention.[15,16]   One particularly jarring anecdote that was recorded in the FDA's *Voice of the Patient* report described a child who was sent back to class by the school nurse after suffering a silent infarct because he was "deemed unruly."[6] We also heard patient testimony of young men being called perverts because they were experiencing priapism.

The appearance of health, coupled with a lack of SCD awareness in patients' broader communities, can lead to ignorant judgments of character. Patients who are unable to participate in their daily commitments at work or school due to unsurmountable fatigue, pain, or other complications, may be accused of laziness or be subject to bullying. Both children and their caregivers felt SCD

> *"My son feels very isolated by sickle cell, and I know he thinks he prevents our family from doing many things because so much of the year we have to stay indoors. He loves to visit places where the temperature is nice and he can easily be outside." – Parent of an individual living with SCD*

challenged their ability to perform well in school and work.[14] Chronic daily pain, fatigue, and the sudden onset of acute pain crises increase absenteeism, make it difficult to concentrate, disrupt school and social interactions and create a lot of stress and anxiety. SCD can cause neurocognitive impairment; some patients have reported difficulty

remembering tasks, retaining what they learn in school, and difficulty staying engaged and focused on school activities.[17-19] Some children reported frustration and social isolation from limitations on their ability to participate in physical activities, travel on long flights, play outside in cold weather, or swim in unheated water. Although SCD is an inherited condition, a lack of societal awareness about the disease leads some patients to hide their diagnoses so that their peers will not misperceive them as contagious.

Family members described the tremendous responsibility of caregiving, including the need to leave the work force to provide care for their loved one while facing the impact of lost wages and significant out-of-pocket expenses. Adult patients reported difficulty in maintaining employment because of frequent, unexpected, or prolonged absences due to acute SCD-related events. Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation. We heard from a number of patients that mental health issues such as depression, anxiety, and suicidal thoughts are common; such statements are corroborated in the clinical literature.[12,14,20]

Racial Bias

We heard consistently, from patients, family members, clinicians, and other members of the sickle

"To improve health care access, the sickle cell community is faced with the awesome task of trying to rewrite the dominant narratives about their patients whose genetic disease marks them in the United States as quintessentially black. This narrative presumes that sickle cell patients are socially dysfunctional, dependent on narcotics, and poorly educated or, worse, uneducable. Knowing only a patient's race or ethnicity, even a well-meaning doctor may make presumptions that influence how he or she communicates with and medically treats a patient."[1] – Rouse, 2009

cell community, that the experience of living with SCD and all aspects of its treatment are mired in racism. Although SCD affects individuals of different races and ethnicities, it has historically been viewed in the US as a "black disease."[1,21] Racism, implicit or otherwise, presents devastating obstacles to care in what is already a debilitating and frequently lethal condition.[1]

We heard frustration from the sickle cell community about the lack of investment in research or comprehensive treatment centers that might increase access to better treatment, improve health outcomes, and reduce other disparities faced by SCD patients and their families. Historically, SCD has been underfunded, with no breakthroughs or developments in two decades. Although the populations of patients living with other severe hereditary

"Consider the fact that we get stigmatized at regular ER hospitals, consider that our bodies work 3 times more than a regular human being, consider that this nation doesn't make sickle cell as a top priority as cancer, leukemia, or AIDS/HIV." – Patient living with SCD

conditions such as cystic fibrosis are significantly smaller than that of SCD, these conditions often receive greater funding for research and treatment. Cystic fibrosis, for example, affects approximately 30,000 people in the US (versus about 100,000 with SCD) and receives 7-11 times the

amount of funding per patient.[15,22,23] Structural racism, as well as implicit bias, affect the allocation of resources toward research, health care delivery, and quality improvement.[24,25]

Pain Relief

Racial bias and treatment disparities are glaringly obvious in the dispensing of analgesics for patients with SCD. Patients who present at emergency rooms in crisis are treated with suspicion.[1,15,26-29] We heard from some patients that they get dressed up in professional attire while in crisis before going to the ER in an effort to avoid categorization as drug seeking. Patients expressed a hesitancy to reveal any familiarity with pain regimens they know to be effective out of fear they would be denied relief or labeled as an addict. We heard that many adult patients have an advocate accompany them on visits to an emergency department to increase their chance of receiving appropriate treatment for pain.

Racial bias in the prescription of pain medications has been well documented. A survey of more than 100 physicians who care for patients with SCD suggested that provider attitudes toward opioid addiction can have negative implications for patients, including undertreatment of pain and discrediting a patient's report of pain severity.[15,27] Furthermore, a 2014 study of attitudes toward patients with SCD among 215 emergency department providers (nurses and physicians) found that relative to physicians, who have less frequent and shorter interactions with patients, nurses had

> *"Most of us aren't coming into the hospitals until the pain is at ridiculous levels because we HATE feeling judged all the time. I don't know what these docs are being taught, but it seems compassion ain't part of the curriculum! […] Most times when describing my pain I don't look at them at all, because if I do and I see that apathetic or judge-y, doubtful look on they face it makes me instantly regret coming in. It's hard because they want you to give eye contact, speak clearly and be so detailed, all of which are incredibly hard when you in pain […]. I've felt like I had to put on a show when I was younger because if I said I'm a 8, 9, or 10 without crying or writhing in pain, they'd never believe me. It was obvious they didn't believe it by how long it would take me to get my medication, or all the tests I'd be forced to take before getting anything for pain." – Patient living with SCD*

greater levels of negative attitudes toward SCD patients; nurses expressed more frustration in caring for patients, estimated a higher prevalence of opioid addiction among patients with SCD, and reported less unease with the ways in which their colleagues treated patients.[15,28]

The ongoing opioid crisis has further complicated patients' ability to access pain medicine, as doctors have grown increasingly wary of over-prescribing addictive therapies. Many state laws, payer coverage policies, and hospital protocols follow "one size fits all" approaches to pain management, which limit dosing or cease dispensing after a predetermined period of time, irrespective of whether an individual's pain is adequately managed. The Centers for Medicare &

Medicaid Services recently issued a policy to recommend that Medicare beneficiaries with SCD be exempt from opioid safety restrictions; similar exemptions have been recommended in some state Medicaid programs, although such policies will not improve patient access if provider attitudes do not also change.[15,30,31]

Lack of Specialists & Competent Treatment

Patients lamented that SCD education and awareness among clinicians, even among hematologists, is severely lacking. Patients commonly receive care from generalists, emergency nurses, and hospitalists, who may be less equipped to help them manage their disease.[15,32,33] We heard repeated concerns that there were not enough doctors and other medical providers who are adequately trained in the management of SCD, particularly for adults. A national survey of over 3,000 family physicians revealed that only 20% of respondents felt comfortable treating SCD.[32,33]

Clinical experts and patients alike commented that incompetent care can be catastrophic; we heard several anecdotes about deaths that might have been prevented had the patient received care from a more knowledgeable provider. Patients are conscious of the deaths and irreversible damage that results from long wait times in the ER, as well as the increased mortality from events that occur in the hospital; they reported feeling intense anxiety and stress about going to the hospital, sometimes delaying or avoiding seeking necessary care. We also heard that some individuals experience post-traumatic stress disorder following severe episodes of illness.

"Too often Sickle Cell Patients are marginalized, treated with stereotypical idealism and inherent bias that ultimately leads to them avoiding going for help or simply not receiving it in their greatest time of need, during the vaso-occlusive crisis. This leads to many damaging side effects including death but more so the damage taking place in their bodies while they are lingering in an untreated state of ongoing necrosis taking place throughout their bodies!" – Patient living with SCD

Among non-specialist providers, we heard there is often the misperception that SCD is a pain condition. This over-simplification can lead to inappropriate care of the disease's many complications. In the ER, treatment with fluids, oxygen, and other medicines may be lacking and patients may be not be appropriately triaged. One caregiver, who was not a trained clinician, told us about needing to adjust a patient's oxygen level while in the hospital out of fear that inadequate attention from the attending providers would prove fatal to the patient.

While the management of pediatric patients with SCD has improved dramatically in recent years, the transition from pediatric to adult care presents a major risk for many patients. There is a significant shortage of adult care providers with the requisite knowledge and skill set. Patients described the difficulty they faced trying to navigate a very different system of care, and recounted a worsening of health as a result of limited access to multi-dimensional care. Indeed, there is a sharp increase in mortality during the transition from pediatric to adult care.[34,35]

> "Finding a great doctor that knows information about sickle cell is finding a needle in a haystack" – Patient living with SCD

This problem is magnified in smaller cities, towns, and rural areas, where patients report needing to travel several hours to see a specialist, participate in a clinical trial, or access treatment through a compassionate use programs. Patients were anxious that the retirement of a community's only specialist would lead to a spike in SCD mortality. A retired specialist from California, Dr. Keith Quirolo, provided some sobering statistics about the severe shortage of sickle cell hematologists: in the state of California, where Dr. Quirolo used to practice, there are only about five physicians who specialize in the treatment of SCD for an estimated 7,000 residents living with the condition.[32]

Attitude Toward New Therapies

There is consensus in the SCD community about the dire need for disease-modifying drugs. Over the past several years, few treatment options aside from analgesia were available. Barriers to accessing and utilizing the few available options, such as pharmaceutical-grade L-glutamine and hydroxyurea are many; these include insufficient payer coverage, a lack of pharmacies that stock these drugs, a lack of awareness among providers about L-glutamine (and reluctance to prescribe it), and patient fears and/or intolerance of undesirable side effects (e.g., running to the bathroom from gastrointestinal side effects of L-glutamine; hair loss or infertility from hydroxyurea). In addition, patients pay out of pocket for supplements commonly recommended for SCD, such as zinc, vitamin B12, chlorophyll, iron, and folic acid.

> "The quality of life for most Sickle Cell Patients is a life of extreme suffering from pain and rejection of medical care. We are stigmatized as drug seekers because there is hardly any tools a care provider can offer us but pain killers. Life is painful and frustrating, and we have few choices in our options for care." – Patient living with SCD

There is cautious optimism about the promising pipeline of therapies, particularly gene therapies, that may soon become available. Nevertheless, patients and families worry about being able to afford expensive new drugs and are concerned that high drug prices may cause insurance policies to implement barriers to access. Patients are concerned that doctors will not

know enough about the new therapies to be willing to write prescriptions for them. Patients also wonder whether they will be eligible for treatment with these new treatments. We heard from some patients that they fear they will be too old or have too much organ damage to be candidates for gene therapy.

Finally, stakeholders emphasized the importance of multidisciplinary care. New therapies need to be integrated into treatment plans that care for the whole patient.

ICER's Methods for Learning about Patient and Caregiver Perspectives

During ICER's scoping and open input periods, we received public comment submissions from 109 stakeholders (82 patients and/or family members of patients, 19 advocacy groups, 2 manufacturers, 1 provider group, 1 clinical society, and 4 clinical experts) and participated in conversations with 19 key informants (3 patients and/or family members of patients, 2 advocacy groups, 3 manufacturers, 1 clinical society, and 9 clinical experts). Following the publication of ICER's draft report, ICER received public comment submissions from 73 stakeholders (28 patients and/or family members of patients, 34 advocacy groups, 4 manufacturers, 6 individuals with expertise in the modeling or treatment of SCD, and 1 clinical society). Collectively, these comments and conversations helped us to draft the narrative described above. The quotations that are integrated into the text above came directly from public comments we received during the scoping phase of this project.

In addition to soliciting public comment and engaging in phone conversations with stakeholders, we also reviewed literature germane to the patient experience. These references are cited in the narrative above.

In order to supplement what we learned from the literature and stakeholder engagement, we collaborated with Sick Cells and the Sickle Cell Disease Association of America (SCDAA) to conduct an online survey of patients and caregivers. The objectives, methods, and results of this survey are described in the section that follows.

SCD Patient and Caregiver Survey

As noted above, ICER collaborated with Sick Cells and the Sickle Cell Disease Association of America (SCDAA) to conduct an online survey. The survey informed our assessment of the comparative effectiveness of new interventions in this review and helped us better quantify important information on quality of life and productivity. Data points from the survey results were also incorporated into the cost-effectiveness model and summarized below.

The goal of the survey was to collect information and perspectives from people living with and who care for people living with SCD. In particular, it captured data not adequately addressed in the literature on the impact of SCD and its complications on ability to work, go to school, or perform usual activities, as well as out-of-pocket costs for treatments and supportive care. Survey questions were both qualitative and quantitative in nature. The full survey can be found in Appendix F.

Methods

The patient advocacy group Sick Cells worked with ICER on all aspects of the survey, from planning to execution. Sick Cells consulted with the clinical, economic, and program teams at ICER on a list of survey questions, and Sick Cells and SCDAA distributed a link to the web-based survey to its members via email, social media, and other methods.

Results

Sick Cells received a total of 547 responses, of which 454 were used in the analysis; 93 responses were excluded because they were from an individual who was not a patient or caregiver, did not reside in the US, or did not answer exclusion questions. The overall completion rate of the survey was 68% (n=309).

Of the 454 included responses, 289 (64%) were patients living with SCD and 165 (26%) were caregivers of patients living with SCD. Because the survey was distributed widely through email and social media, we were not able to calculate a response rate.

Figure 2.1 Survey Response Characteristics

| 547 Total responses | → | 93 Excluded
• 46 did not answer screening questions
• 24 were not a patient or caregiver
• 15 do not reside in the US | → | 454 Included in analysis
• 289 patients
• 165 caregivers |
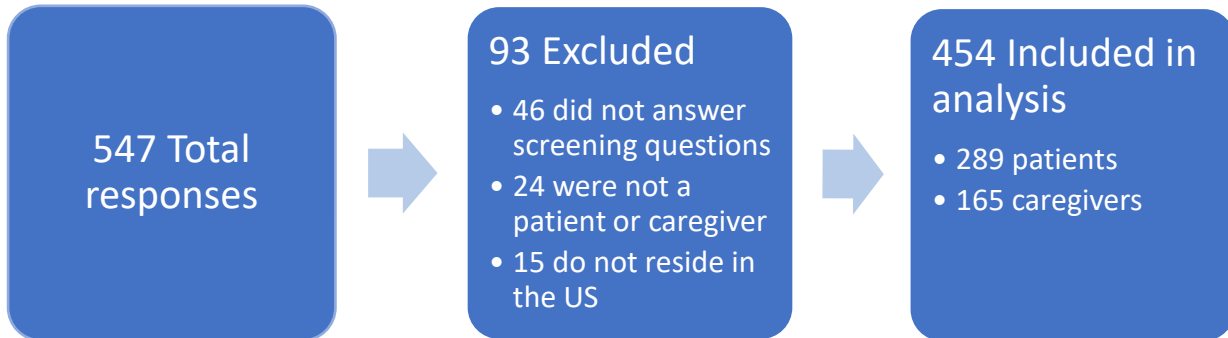
Demographics

Of the caregivers, the majority (77%) reported that they were the parent or grandparent of a person living with SCD.

Table 2.1. Caregiver Relationships

For Caregivers (N=165): What is your relationship to the person you care for?	
Relationship	N (%)
They are my child or grandchild	127 (77.4%)
They are my spouse or partner	11 (6.4%)
They are another family member	16 (9.8%)
They are my parent or grandparent	6 (3.7%)
Other	4 (2.4%)

The demographics of the survey respondents is reported in Table 2.2. The average age of patients in the sample was 32.5 years (range 1-80). Most respondents were female (70%) and African American (94%).

Table 2.2. Survey Demographics

Respondent Demographics (N=454)	
Age (of person living with SCD), Mean (range)	32.5 (1-80)
Gender (of person living with SCD)	Female: 321 (70.6%) Male: 127 (28.0%) Non-binary: 6 (1.4%)
Race and Ethnicity (of person living with SCD) **Note: because respondents could select more than 1 category, percentages add up to more than 100%**	African American: 427 (94.1%) Hispanic: 23 (5.1%) White: 10 (2.2%) American Indian or Alaskan Native: 5 (1.1%) Middle Eastern or Northern African: 3 (0.7%) Asian or Pacific Islander: 1 (0.3%) Other: 13 (2.9%) I prefer not to answer: 2 (0.4%)

The health insurance status of the survey respondents is below in Figure 2.2. Commercial insurance through work, school, or parents or through the state exchange (36.3% and 4.6% respectively) was reported most frequently, followed by Medicaid (33.5%) and Medicare (18.9%).

Figure 2.2. Health Insurance Status

Primary source of health insurance for patients with SCD (n=454)
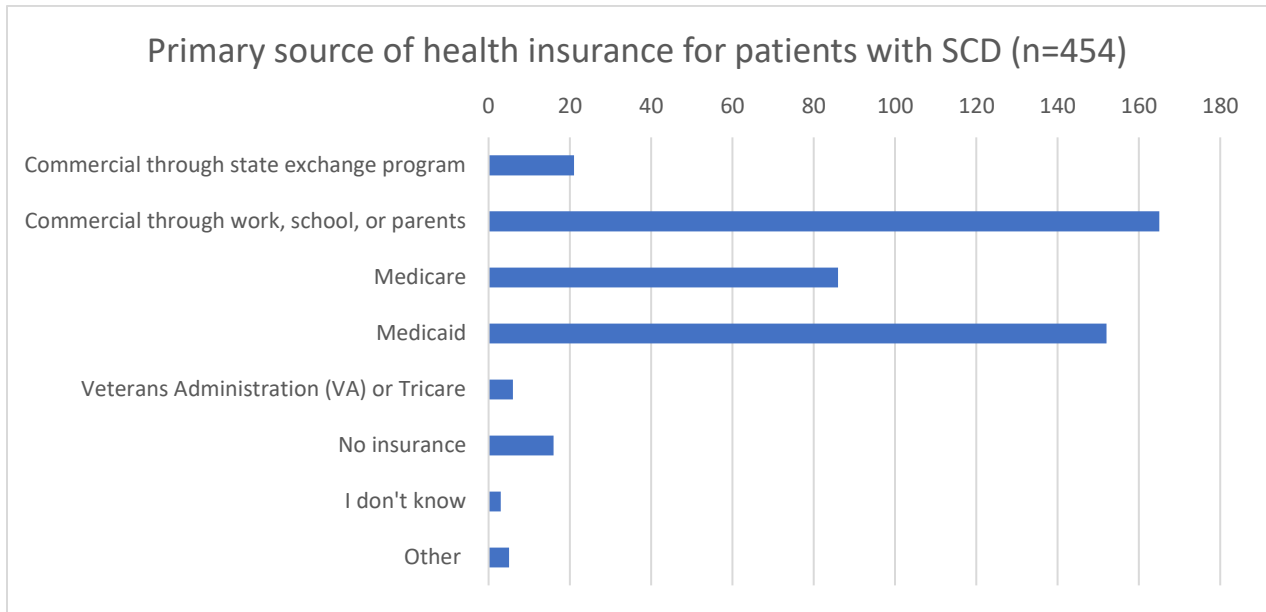
Health Effects of Sickle Cell Disease

Respondents indicated that sickle cell disease affected their lives in a variety of ways (Figure 2.3). Chronic pain (63%) and fatigue (58%) were most the commonly cited health effects, followed by cognitive impairment (14%) and iron overload (10%).

Figure 2.3. Health Effects of Sickle Cell Disease
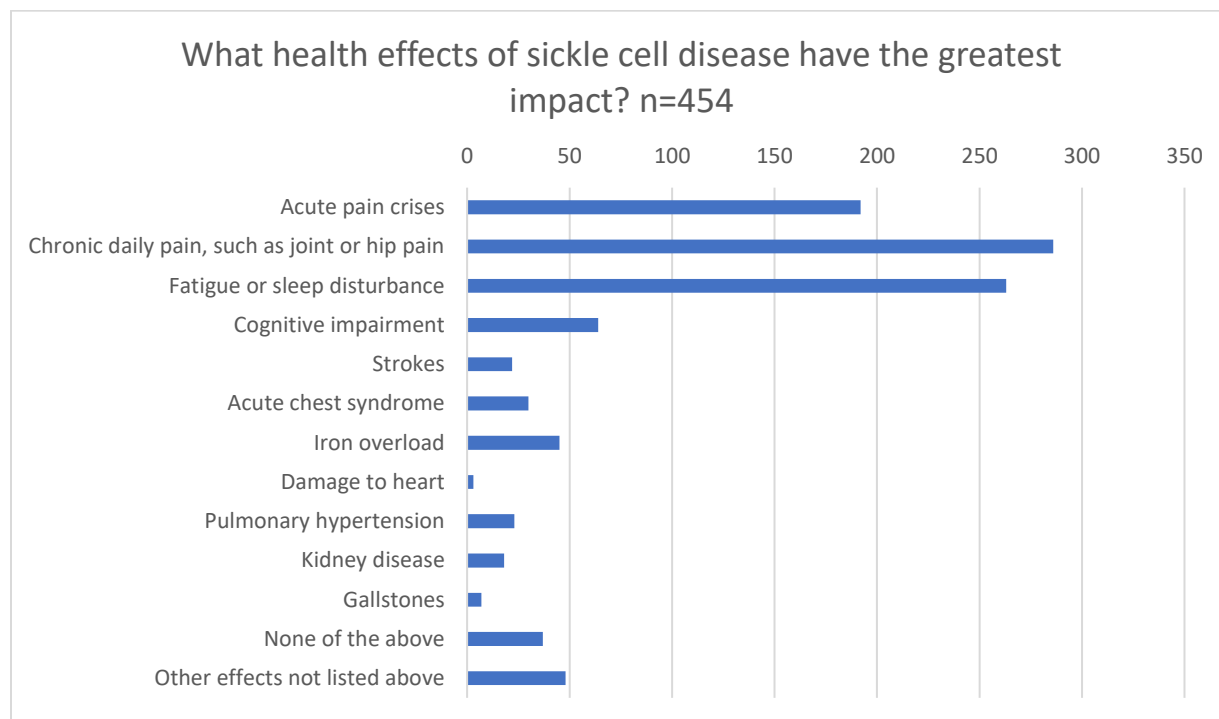
Patients and caregivers reported that they experienced a mean of 12.6 pain crises per year. Of those pain crises, about half (6.1) required medical attention. There was wide variability in the estimates for both the number of pain crises (SD=20.5) and the number requiring medical attention (SD=8.0).

Table 2.3. Frequency of Pain Crises

Frequency of Pain Crises	Pain crises, N, mean (SD) (N=370)
Pain crises experienced last year (SD)	12.6 (20.5)
Pain crises requiring medical attention (SD)	6.1 (8.0)

Patients and caregivers were most likely to report that their last pain crisis lasted more than 4 days (46.5%), followed by 3-4 days (26.4%) (Figure 2.4). Respondents reported that they were not able to work, go to school, do physical activities or social activities for 4 to 7 days on average during their most recent pain crisis (Table 2.4).

Figure 2.4. Duration of Pain Crises

How long did your most recent pain crisis last? n=370

Table 2.4. Impact of Pain Crises on Usual Activities

During your most recent pain crisis, how many days were you unable to do the following?:	
Work (average)	4.8
Go to school (average)	4.2
Do physical activity (average)	6.7
Do usual social activities (average)	6.5

Treatments

Prescription pain medications (such as codeine, morphine or dilaudid) were the most commonly used treatment to manage sickle cell disease complications, followed by over-the-counter pain medications, hydroxyurea and IV hydration.

Table 2.5. Treatments for Sickle Cell Disease

What treatments have you used in the last month to manage sickle cell disease and its complications? Select all that apply.	
Treatment	**All respondents, N (%)**
Prescription pain medications (such as codeine, morphine or dilaudid)	236 (69.6%)
Over the counter pain medications (such as ibuprofen, Tylenol or Aleve)	200 (59%)
Hydroxyurea	166 (49%)
IV Hydration	109 (32.2%)
Simple blood transfusion	77 (22.7%)
Exchange transfusion (RBC apheresis)	47 (13.9%)
Prescription L-glutamine (Endari)	44 (13.0%)
Voxelotor (Oxbryta)	5 (1.5%)
Crizanlizumab (Adakveo)	2 (0.6%)
No treatment	19 (5.6%)
Other	50 (14.7%)

Out of Pocket Costs

Respondents reported significant monthly out-of-pocket costs for a variety of services. Medical appointments and hospitalizations were the highest out-of-pocket costs on average ($150/month), followed by transportation ($55/month), medications ($54/month), paid caregivers ($49/month), and pain management ($48/month). There was wide variability in these estimates so true out of pocket costs may be significantly different.

Table 2.6 Out-of-Pocket Costs for Medical and Other Services

Item	Monthly out of pocket cost ($), mean (SD)
Medical appointments and hospitalizations related to sickle cell disease	$150 ($702)
Transportation, parking, and other accommodations for medical appointments and hospitalizations (such as meals and child care)	$55 ($128)
Medications (both prescription and over the counter)	$54 ($85)
Paid caregivers or support services (such as for care in the home, housework, errands, etc.)	$49 ($240)
Pain management techniques (such as massage, yoga, meditation, etc.)	$48 ($132)
Vitamins or nutritional supplements	$38 ($56)
Mental health services	$31 ($134)
Medical supplies (such as wheelchairs, canes, bandages, wound care, oxygen equipment, etc.)	$30 ($127)
Other out-of-pocket costs	$18 ($55)

Employment

When asked if they were currently working, 220 patients or caregivers of patients with sickle cell disease (49%) responded that they were not currently employed (working for pay) and 231 (51%) were working for pay. When asked why, the most common reason for being unemployed was the difficulty working due to hardships (especially disability) from the disease, the time needed to care for a person with sickle cell disease, followed by being a student, or stay-at-home parent.

Among the respondents who were currently working, they reported working an average of 29.7 hours in the last week and missing an average of 9.2 hours of work due to sickle cell disease.

The Work, Productivity, and Activity Impairment (WPAI) instrument, is a publicly-available, validated 5-item measure of productivity and activity limitations for specific health conditions http://www.reillyassociates.net/WPAI_SHP.html. Higher scores represent greater levels of impairment due to a health condition. Respondents reported an overall 65% work impairment due to sickle cell disease.

Table 2.7 Work, Productivity, and Activity Impairment (WPAI)

WPAI-SHP Score	
Work time missed due to SCD (Absenteeism)	23.7%
Impairment while working due to SCD (Presenteeism)	44.6%
Overall work impairment due to SCD (Work productivity loss)	65.1%
Activity impairment due to SCD (Activity impairment)	54.2%

WPAI: Work, Productivity, and Activity Impairment

Summary

The SCD patient and caregiver survey provided a rich picture of the impact of SCD on patients and their caregivers. The respondents were majority female (70%) and African American (94%) and suffered from acute or chronic pain and fatigue. Pain crises were common, lasting more than four days and significantly impacted their ability to work, go to school, or participate in usual activities. Prescription or over the counter pain medication use was high as were monthly out of pocket costs. Overall work productivity loss was high (65%). These results are similar to a recent study evaluating the impact of acute pain crises on work, productivity, and quality of life in SCD patients[60]. Given these findings, it is not surprising that about half were unemployed, most commonly as a result of the disability caused by the disease or the time and effort to care for a person with SCD. It should be noted that the risk of recall and selection bias is high for an online survey using a convenience sample. Nevertheless, these results underscore the need for more research to demonstrate the impact of treatments of SCD on quality of life and ability to work.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

For our review of crizanlizumab (Adakveo), voxelotor (Oxbryta), and pharmaceutical grade L-glutamine (Endari)'s insurance coverage, we reviewed publicly-available coverage policies for US national and regional commercial payers (Aetna, Anthem, Blue Cross Blue Shield Massachusetts [BCBSMA], CareFirst, Cigna, Emblem, and UnitedHealthcare) and public plans of MassHealth (Massachusetts Medicaid), Neighborhood Health Plan of Rhode Island (Rhode Island Medicaid), New Hampshire Department of Health and Human Services (New Hampshire Medicaid), Florida Medicaid, and Texas Medicaid.

This report version has been updated to include the recently added commercial and public policies for crizanlizumab and voxelotor.

Crizanlizumab

Of the seven surveyed commercial payers, Anthem, BCBSMA, Emblem, and UnitedHealthcare cover crizanlizumab according to the criteria specified in Table 3.1.[61-64] Age and diagnosis criteria are consistent across all payers; initial authorization and renewal criteria vary slightly (Table 3.1). Emblem and UnitedHealthcare both restrict coverage to patients concurrently receiving hydroxyurea therapy while BCBSMA and UnitedHealthcare also restrict coverage to those receiving chronic blood transfusions.[62,64] In addition, BCBSMA requires patients to have hemoglobin level > 4.0 g/dL and UnitedHealthcare requires a hematologist or other SCD specialist to prescribe the medication.[62,64] Cigna has prior authorization requirements for crizanlizumab but did not have these criteria publicly available.[65]

Of the five public plans, only Florida and Texas Medicaid had publicly-available policies with prior authorization criteria for crizanlizumab, and both resembled that of Anthem's.[66,67]

Table 3.1. Private and Public Coverage Restrictions and Specifications for Crizanlizumab

	Age	Diagnosis & Clinical Criteria	Prescriber Criteria	Other Clinical Criteria	Dosing	Initial Authorization Duration	Renewal Criteria
Anthem[63]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	NA	According to FDA label*	NA	NA
BCBSMA[64]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	Not receiving RBC transfusion therapy; hemoglobin >4.0 g/dL	NA	6 months	Proof of the decrease or continued decreased of VOCs from the original 6-month
Emblem Health[61]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	On a stable dose of hydroxyurea for at least 3 months, with hydroxyurea prescribed for at least 6 months	According to FDA label*	12 months	Meet initial approval criteria, absence of unacceptable toxicity from drug =, and improvement or stabilization of disease (e.g., reduction in VOCs)
UnitedHealthcare[62]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	Prescribed by hematologist or other specialist with SCD expertise	Currently receiving hydroxyurea or failure, intolerance, **or** contraindication to hydroxyurea; not receiving chronic blood transfusions and not receiving voxelotor	According to FDA label*	6 months	Meet initial approval criteria, and reduction in VOCs and/or decrease in severity of VOCs from pretreatment baseline

	Age	Diagnosis & Clinical Criteria	Prescriber Criteria	Other Clinical Criteria	Dosing	Initial Authorization Duration	Renewal Criteria
Florida Medicaid[66]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	NA	According to FDA label*	12 months	NA
Texas Medicaid[67]	≥16 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	NA	According to FDA label*	NA	NA

FDA: Food and Drug Administration, NA: not available, SCD: sickle cell disease, RBC: VOC: vasoocclusive crisis

*5mg/kg intravenously over 30 minutes at week 0, and week 2, then every 4 weeks thereafter

We were unable to locate a policy for CareFirst.

Voxelotor

The majority of the surveyed commercial plans covered voxelotor, however, only Anthem and BCBSMA had publicly available policies (Table 3.2). Anthem and BCBSMA cover voxelotor for patients aged 12 or older with a diagnosis of SCD and not receiving chronic transfusion therapy.[64,68] BCBSMA specified that patients' hemoglobin level should fall between 5.5 and 10.5 g/dL while Anthem requires that patients have two or more sickle cell-related pain crises in the last 12 months, and no severe renal dysfunction as defined in the table below.[64,68] For patients seeking combination therapy with hydroxyurea, Anthem restricts coverage to those receiving a stable dose of hydroxyurea for at least three months.[68] Cigna does not cover voxelotor unless approval is granted through a request for exception and CareFirst did not have a publicly available coverage policy.[65]

Of the public payers, only Florida and Texas Medicaids had publicly available coverage policies for voxelotor (Table 3.2). Florida Medicaid specified clinical criteria of having at least one sickle cell-related pain crisis within the last year, not receiving prophylactic blood transfusion therapy, and a baseline hemoglobin range matching that of BCBSMA's.[69] In addition, Florida Medicaid required the medication to be prescribed by a hematologist or other SCD specialist.[69] Texas Medicaid covered voxelotor for patients aged 12 or older who were diagnosed with SCD in the last 730 days and not on a CYP3A4 substrate in the last 45 days in accordance with a number of quantity limits specified in Table 3.2's footnotes.[70]

Table 3.2. Private and Public Coverage Restrictions and Specifications for Voxelotor

	Age	Diagnosis & Clinical Criteria	Prescriber Criteria	Other Clinical Criteria	Initial Authorization Duration	Renewal Criteria
Anthem[68]	≥12 years	Diagnosis of SCD **and** 2 or more sickle cell-related pain crises within past 12 months	NA	If individual continues using in combination with hydroxyurea, the hydroxyurea dose must be stable for at least 3 months; not receiving chronic transfusion therapy; no severe renal dysfunction defined as <30 mL/min/1.73 m2 or on chronic dialysis	1 year	NA
BCBSMA[64]	≥12 years	Diagnosis of SCD	NA	Not receiving chronic transfusion therapy; hemoglobin (Hb) ≥5.5 and ≤10.5 g/dL	6 months	Documentation including proof of the increase of hemoglobin of >1.0 g/dL from the original 6-month period or continued hemoglobin increase achieved from the original 6-month period
Florida Medicaid[64]	≥12 years	Diagnosis of SCD **and** at least one sickle cell-related pain crisis within past 12 months	Prescribed by or in consultation with a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease.	Patient is not receiving prophylactic blood transfusion therapy; Baseline hemoglobin range is ≥ 5.5 g/dL and ≤ 10.5 g/dL	NA	One of the following: Increase in hemoglobin by ≥ 1g/dL from baseline or decrease in the number of sickle cell-related VOCs or decrease in percent reticulocyte count from baseline or decrease in indirect bilirubin count from baseline

	Age	Diagnosis & Clinical Criteria	Prescriber Criteria	Other Clinical Criteria	Initial Authorization Duration	Renewal Criteria
Texas Medicaid[70]	≥12 years	Diagnosis of sickle cell disease in the last 730 days		Not on a CYP3A4 substrate with a narrow therapeutic index in the last 45 days; quantity limits*	1 year	NA

NA: not available, SCD: sickle cell disease

MassHealth, New Hampshire Medicaid, and Rhode Island Medicaid did not have publicly available policies

*Severe hepatic impairment: no more than 2 tablets/day; on a strong or moderate CYP3A4 inducer in the last 45 days: no more than 5 tablets/day; on a strong CYP3A4 inhibitor or fluconazole in the 45 days: no more than 2 tablets per day

Pharmaceutical Grade L-Glutamine

Excluding Cigna, the remaining six of the seven surveyed commercial payers covered L-glutamine for SCD with varying prior authorization criteria (Table 3.3). CareFirst, Anthem, and BCBSMA require prior authorization for L-glutamine, and Anthem and BCBSMA specify coverage as a tier three option, but their policies were not publicly available.[71-73] We were only able to locate publicly-available coverage policies for Aetna, Emblem, and UnitedHealthcare– all of whom specified a patient age restriction of 5 years or older for coverage. [74-76] Emblem covered L-glutamine for all FDA approved indications[77] (i.e., SCD patients 5 years of age or older) while Aetna and UnitedHealthcare also required that the patient have experienced two or more painful sickle cell crises within the last year.[74-76] Emblem and UnitedHealthcare required a SCD specialist or hematologist, respectively, to prescribe L-glutamine.[75,76] Aetna restricted coverage to those who showed a documented contraindication or failure of hydroxyurea while UnitedHealthcare required both a history of failure to non-prescription L-glutamine supplementation and also concurrent use of or contraindication to hydroxyurea.[74,76] All payers offered initial coverage for 12 months duration, with Aetna and UnitedHealthcare specifying positive or improved clinical response for reauthorization.[74-76]

Of the public payers we surveyed for this report, only MassHealth had a publicly-available coverage policy (Table 3.3).[78] Similar to the commercial payers, MassHealth covered L-glutamine for patients with a diagnosis of SCD, five years of age or older, having experienced two or more painful sickle cell crises in the last year.[78] Coverage was restricted to those having inadequate or contraindicated response to hydroxyurea, and no prescriber criteria were specified.[78] Initial duration of coverage spanned 12 months and no criteria were specified for reauthorization.[78]

Table 3.3. Private and Public Coverage Restrictions and Specifications for L-Glutamine

	Age	Diagnosis & Clinical Criteria	Prescriber Criteria	Other Clinical Criteria	Initial Authorization Duration	Renewal Criteria
Aetna[74]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	NA	A documented contraindication, intolerance, allergy, or failure of hydroxyurea	12 months	Clinical documentation indicating disease stability or improvement from baseline
Emblem Health[75]	≥5 years	All FDA approved indications not otherwise excluded from Part D	Prescribed by, or in consultation with, a physician who specializes in SCD	NA	12 months	NA
UnitedHealthcare[76]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	Prescriber is a hematologist	History of failure to non-prescription L-glutamine supplementation **and** Using concurrent hydroxyurea or unable to take hydroxyurea due to contraindication/intolerance	12 months	Documentation of positive clinical response to therapy
MassHealth[78]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	NA	Inadequate response, adverse reaction, or contraindication to hydroxyurea	12 months	NA

NA: not available, SCD: sickle cell disease

CareFirst[71], Anthem[72], and Blue Cross Blue Shield of Massachusetts (BCBSMA)[73] require prior authorization for L-glutamine but their policies were not publicly available.

Cigna does not cover L-glutamine.

3.2 Clinical Guidelines

American Society of Hematology (ASH)

2020 Guidelines for Sickle Cell Disease: Transfusion Support[79]

A multidisciplinary guideline panel formed by ASH agreed on 10 recommendations for the screening, prevention, and management of iron overload, alloimmunization, and delayed hemolytic transfusion reactions (DHTRs).

Before the first transfusion or at the earliest opportunity, the panel suggests obtaining an extended red cell antigen profile by genotype or serology for all SCD patients and recommends prophylactic red cell antigen matching for Rh and K antigens for those receiving transfusions. The panel suggests immunosuppressive therapy in SCD patients with an acute need for transfusion and who are at increased risk of acute hemolytic transfusion reactions or with a history of multiple or DHTRs and ongoing hyperhemolysis.

For SCD patients receiving chronic transfusions, the panel suggests using automated red cell exchange (RCE) transfusions rather than simple or manual RCE; either conventional RCE or RCE with isovolemic hemodilution is recommended for this population. In addition, the panel suggests iron overload screening for liver iron content by magnetic resonance imaging (MRI) every one to two years.

For patients with severe acute chest syndrome (ACS), the panel suggests automated transfusion over manual RCE and in those with moderate ACS, the panel suggests automated RCE, manual RCE or simple transfusion methods.

For pregnant patients with SCD, the panel suggests either standard care or prophylactic transfusion at regular intervals. More broadly, for patients with SCD undergoing surgery requiring general anesthesia or lasting more than an hour, preoperative transfusion is suggested.

American Society of Hematology (ASH)

2019 Guidelines for Sickle Cell Disease: Cardiopulmonary and Kidney Disease[80]

A multidisciplinary guideline panel formed by ASH agreed on 10 recommendations to support the screening, diagnosis, and management of SCD and its cardiopulmonary and renal complications. Due to a lack of direct, high-quality evidence on the SCD outcomes of interest, the majority of recommendations were conditional rather than strong. Although these recommendations advise on management of patients with pulmonary arterial hypertension, albuminuria, unprovoked venous thromboembolism, and sleep-disordered breathing, we have summarized only the two

recommendations pertaining to outcomes relevant to our review: chronic kidney disease (CKD) and management with hydroxyurea.

The panel suggests referral for a renal transplant for those with advanced CKD or end-stage renal disease. For those with worsening anemia associated with CKD, the panel suggest combination therapy with hydroxyurea and erythropoiesis-stimulating agents.

National Heart, Lung, and Blood Institute (NHLBI)

Evidence-Based Management of Sickle Cell Disease: Expert Panel, 2014[7]

The NHLBI convened a multidisciplinary panel to develop guidelines for the management, recognition, and treatment of acute and chronic complications of SCD, for patients ranging from infancy through adulthood. These guidelines cover an extensive list of recommendations and for the purpose of this report, we have summarized only those which are most strongly recommended and focus on the outcomes and management options related to our review: acute pain crisis, ACS, acute and chronic transfusion, hemoglobin, hydroxyurea, and stroke.

Health Maintenance (with focus on outcomes listed above)

- Only in children with sickle cell anemia (SCA; does not include those with HbSC, HbSD, HbSβ^0 thalassemia, or HbSβ$^+$ thalassemia), from age two through at least 16, the panel strongly recommends annual screening with transcranial doppler (TCD) imaging for the risk of stroke.

Management of Acute Complications of SCD (with focus on outcomes listed above)

- The panel strongly recommends treatment with parenteral opioids for adults and children experiencing an acute pain crisis with severe pain.
- For those hospitalized for an acute pain crisis, the panel recommends incentive spirometry while awake to reduce the risk of ACS.
- For patients who have ACS, the panel strongly recommends treatment with 1) intravenous cephalosporin, 2) an oral macrolide antibiotic, 3) supplemental oxygen, and 4) monitoring for hypoxemia, acute anemia, and bronchospasm.
- Among all patients, when there is rapid progression of ACS, the guidelines recommend urgent exchange transfusion and use of incentive spirometry while awake.

Hydroxyurea Therapy for Management of SCD (with focus on outcomes listed above)

- The panel strongly recommends treatment with hydroxyurea among adults with SCA for all of the following: those who have at least three moderate to severe pain crises within a year,

those whose pain interferes with daily activities and quality of life, those who have a history of severe and/or recurrent ACS, and those who have severe symptomatic chronic anemia.

- For infants at least nine months of age, and children and adolescents with SCA , treatment with hydroxyurea to reduce SCD-related complications is recommended regardless of clinical severity.

Blood Transfusions for Management of SCD (with focus on outcomes listed above)

- Prior to undergoing a surgical procedure, the guidelines state that all adults and children with SCA are to be transfused with red blood cells to raise hemoglobin level to 10 g/dL.
- For both children and adults, the guidelines suggest consulting a blood bank for a workup of possible delayed hemolytic transfusion reaction (DHTR), for patients showing signs of acute anemia, jaundice, or pain within three weeks after a blood transfusion.
- For patients receiving chronic transfusion therapy, the guidelines recommend performing serial assessment of iron overload.
- In children with TCD results >170 cm/sec, the guidelines recommend referral to a specialist who may initiate chronic transfusion therapy for the prevention of stroke.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the clinical effectiveness of crizanlizumab, voxelotor, and L-glutamine in the treatment of SCD, we sought evidence related to each of these therapies in comparison with optimal usual care. We did not attempt to compare the interventions to each other, as these therapies may have a complementary role in the management of SCD. Our review focused on clinical benefits (i.e., mortality, acute pain crisis, organ damage, and quality of life), as well as potential harms (drug-related adverse events [AEs]). Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on crizanlizumab, voxelotor, and L-glutamine for SCD followed established best research methods.[81,82] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[83] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, and Comparator elements described in Section 1.2. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms (see Appendix Tables A2 and A3).

To supplement the database searches, we performed manual checks of the reference lists of included trials and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all identified publications using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix D). Elements included a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[84]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included sickle cell, crizanlizumab, voxelotor and L-glutamine. We searched for studies which would have met our inclusion criteria, and for which no findings have been published.

Data Synthesis and Statistical Analyses

The results of included studies are described narratively in the sections that follow. Analyses are descriptive in nature only, as we did not intend to compare crizanlizumab, voxelotor, and L-glutamine to each other through indirect quantitative analysis. Insufficient data were identified to allow for pairwise meta-analyses of individual agents.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among crizanlizumab, voxelotor, and L-glutamine relative to optimal supportive care (see Appendix D).[85]

4.3 Results

Study Selection

Our literature search identified 103 potentially relevant references (see Appendix Figure A1), of which 14 references (5 publications, 6 conference presentations, and 3 FDA Multidisciplinary Review packets) relating to 4 individual studies met our inclusion criteria. The primary reasons for study exclusion included interventions or dosing protocols not of focus and evaluation of outcomes not of interest (e.g., red cell nicotinamide adenine dinucleotide redox potential).

Of the 11 included references, 5 references related to a single Phase II RCT of crizanlizumab.[36,86-89] We identified a single publication of a Phase III RCT of voxelotor and 3 conference abstracts related to the same trial; earlier phase studies of voxelotor were excluded due to the use of lower doses of the drug.[37] We included 4 references of L-glutamine, which corresponded to a Phase II and a Phase III RCT.[9,38,90,91] Details of all included studies are summarized in Appendix D and in the sections that follow.

Although we defined several chronic SCD complications (e.g., chronic pain, organ damage, mortality) in our scope as outcomes of interest, we did not identify any data related to the effect of crizanlizumab, voxelotor, or L-glutamine on these outcomes. Consequently, the results described below summarize the short-term treatment effects of these therapies, including acute complications (e.g., incidence of acute pain crises, ACS), health care utilization (e.g. hospitalizations and emergency department visits), quality of life, and changes in hemolysis markers).

Quality of Individual Studies

We rated the key studies of crizanlizumab and voxelotor to be of good quality using criteria from the USPSTF (Appendix D).[36,37] The trials had adequate blinding of patients, investigators, and outcome assessors. The groups were comparable at baseline and there was non-differential follow-up. We rated the Phase III trial of L-glutamine to be fair quality because there was a high and different loss to follow-up between groups; statistical imputation to account for these differences may have introduced further bias.[9] We considered the Phase II trial of L-glutamine to be poor quality because of differences in the groups assembled at baseline, a large and differential rate of drop-out, and inadequate control for potential confounders (e.g., hydroxyurea use).[90]

Assessment of Publication Bias

As described in our methods, we searched for studies which would have met our inclusion criteria, and for which no findings have been published. We identified two unpublished studies of L-glutamine, one of which was terminated early because it did not reach the targeted enrollment of 50 participants, and another that had insufficient data for the primary endpoint analysis due to a

high rate of discontinuation. We have summarized the limited information we have for these two studies in Appendix Table D18.

Key Studies of Crizanlizumab

Evidence on crizanlizumab was derived from the SUSTAIN trial.[36] This study was a Phase II, placebo-controlled trial that randomized 198 individuals with SCD to 5.0 mg/kg of crizanlizumab (n=67), 2.5 mg/kg of crizanlizumab (n=66), or placebo (n=65). The trial included a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase. Crizanlizumab was administered intravenously in two loading doses, two weeks apart, and every 4 weeks thereafter through week 50 of the trial (14 total doses). As crizanlizumab was approved at the higher dose (5.0 mg/kg), efficacy data pertaining to the low-dose arm of SUSTAIN was not summarized in this review. Safety data were supplemented with evidence from the low-dose arm.

Patients 16-65 years of age were eligible to participate in SUSTAIN if they had any genotype of SCD and experienced 2-10 SCD-related acute pain crises in the 12 months prior to enrollment.[36] Patients who had been receiving treatment with hydroxyurea for at least six months and had maintained a stable dose during the three months immediately preceding enrollment, were permitted to continue therapy during the trial; receipt of chronic red-cell transfusions was an exclusion criterion.

At baseline, patient characteristics were balanced across intervention arms. Patients in the crizanlizumab group had a median age of 29 years, 52% were females, 90% were black, 70% had an HbSS SCD genotype, and 63% were receiving concomitant therapy with hydroxyurea.[36] The proportion of patients with 2-4 or 5-10 SCD-related crises in the previous year, was 63% and 37%, respectively (Table 4.1).

Table 4.1. Key Trial of Crizanlizumab: SUSTAIN[36]

Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
1. Crizanlizumab (5 mg/kg, N=67) **2. Crizanlizumab** (2.5 mg/kg, n=66)‡ **3. Placebo** (N=65)	16 – 65 years of age SCD diagnosis (any genotype) 2-10 acute pain crises in 12 months before enrollment	52-weeks of treatment + 6-week evaluation phase **Early discontinuation** Crizanlizumab: 36% Placebo: 37%	**Median age**: 29 years (range 16-63) **Black**: 90% **HbSS**: 70% **HbSC**: 13% **HbSβ0**: 4% **HbSβ+**: 10% **Other**: 1% **Hydroxyurea use**: 63% **Acute pain crises in prior 12 months**: 2-4: 63%, 5-10: 37%	Annual rate of acute pain crises Acute episodes of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a medical facility visit and treatment with oral or parenteral agents or with a parenteral nonsteroidal anti-inflammatory drug.

SCD: sickle cell disease

*Baseline Characteristics reported from crizanlizumab 5 mg/kg arm. Baseline characteristics were balanced across treatment arms; ‡ evidence pertaining to efficacy of low-dose crizanlizumab was not summarized in this report, however we supplemented our safety review with data from this dosage arm.

The SUSTAIN trial's primary endpoint was the annual rate of sickle cell-related pain crises, defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug.[36] Acute chest syndrome (ACS), hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered to be crisis events.

Clinical Benefits of Crizanlizumab

Compared to optimal usual care alone (i.e., placebo), patients treated with crizanlizumab experienced fewer acute pain crises per year and sustained a longer period of time before the first (and second) crises following initiation of the trial therapy. The annual rate of days hospitalized was numerically lower with crizanlizumab, although this outcome did not reach statistical significance. Crizanlizumab did not improve quality of life, as measured in the study.

Acute Complications of SCD

As noted above, SUSTAIN evaluated the annual rate of sickle cell-related acute pain crises as its primary endpoint. The median annualized crisis rate was 1.63 in the crizanlizumab group and 2.98 in the placebo group (median difference -1.01, p=0.01).[36] Time to event analyses suggested that

crizanlizumab reduced the risk of a first and second acute pain crisis by approximately 50% (Table 4.2).

Uncomplicated crises, defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism, occurred at a median rate per year of 1.08 (IQR 0.00-3.96) in patients treated with crizanlizumab, compared to a rate of 2.91 (IQR 1.00-5.00; p=0.02) in the placebo arm.[36]

The median rate of ACS did not statistically differ across treatment arms, as all groups had a rate of zero.[36] At the end of the treatment phase, 36% of the crizanlizumab group had a crisis rate of zero, compared to 18% of the placebo group.[36]

Table 4.2. Acute SCD Complications in the SUSTAIN Trial of Crizanlizumab[36,87]

	Crizanlizumab (n=67)	Placebo (n=65)	p-value
Annual rate of acute pain crises per year, Median (IQR)	1.63 (0.00-3.97)	2.98 (1.25-5.87)	Median difference:* -1.01 (95% CI (-2.00 to 0.00) p=0.01
Patients with crisis rate of zero, n (%)	24 (35.82)	11 (16.92)	p=0.013
Time to first acute pain crisis, Median months (IQR)	4.07 (1.31-NR)	1.38 (0.39-4.90)	p=0.001
Time to first acute pain crisis, HR (95% CI)	0.50 (0.33 to 0.74)		
Time to second acute pain crisis, Median months (IQR)	10.32 (4.47-NR)	5.09 (2.96-11.01)	p=0.02
Time to second acute pain crisis, HR (95% CI)	HR 0.53 (0.33 to 0.87)		
Annual rate of uncomplicated acute pain crises, Median (IQR)	1.08 (0.00-3.96)	2.91 (1.00-5.00)	p=0.02
Annual rate of ACS, Median (IQR)	0 (0.00-0.00)	0 (0.00-0.00)	p=0.78

ACS: acute chest syndrome, CI: confidence interval, HR: hazard ratio, IQR: interquartile range, NR: not reported, SCD: sickle cell disease, *Median difference and CI estimated using Hodges-Lehmann method

Hospitalization

The median rate of days hospitalized per year was 4.0 (IQR 0.0-25.7) in the crizanlizumab group and 6.9 (IQR 0.0-28.3) in the placebo group; this difference did not reach statistical significance.[36] A post-hoc time to event analysis also did not reach statistical significance but suggested that crizanlizumab may have delayed time to first hospitalization (median 6.3 vs. 3.2 months for the crizanlizumab and placebo arms, respectively; HR 0.68 [95% CI 0.44 to 1.07]).[86]

Table 4.3. Hospitalizations in the SUSTAIN Trial of Crizanlizumab[36,86,88]

	Crizanlizumab (n=67)	Placebo (n=65)	Difference p-value
Annual rate per year of days hospitalized, Median (IQR)	4.0 (0.0-25.7)	6.9 (0.0-28.3)	Median: 0.0 (95% CI -4.4 to 0.0) p=0.45
Patients with ≥1 hospitalization, n (%)	36 (54)	42 (65)	NR
Median time to first hospitalization (months)	6.3	3.2	NR
Time to first hospitalization	HR: 0.68, 95% CI (0.44 to 1.07)		

CI: confidence interval, HR: hazard ratio, IQR: interquartile range, NR: not reported

Quality of Life

The SUSTAIN trial evaluated quality of life using the Brief Pain Inventory (BPI) Questionnaire and the 36-Item Short Form Survey (SF-36) as exploratory endpoints. The BPI is a patient-reported instrument to rate the severity of a patient's pain and its impact on daily function. Statistically significant changes from baseline in BPI scores were not observed during the SUSTAIN trial.[36]

The SF-36 is a general patient-reported quality of life instrument that measures patients' perceptions of health and well-being along 8 scales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to personal or emotional problems, and mental health. Significant differences in the LS mean change from baseline to Week 52 were not observed in any of the domains of the SF-36, including the bodily pain scale.[88]

Markers of Hemolysis

No significant differences were observed in changes in hemoglobin, lactate dehydrogenase, number of reticulocytes, haptoglobin, and indirect bilirubin between the crizanlizumab and placebo arms of the SUSTAIN trial.[36]

Subgroup Analyses

Treatment with crizanlizumab resulted in a lower rate of acute pain crises across a number of subgroups of interest, including groups characterized by concomitant hydroxyurea use, the number of pain crises in the prior year, and sickle cell genotype. Table 4.4 reports the median annual rate of pain crises in these groups; additional outcomes in these subgroups, including the proportion of patients who were crisis free, time to first and second crisis, and type of crisis are reported in Appendix Table D4. Interaction tests to assess whether treatment efficacy differed between subgroups were not reported.

Table 4.4. Annual Rate of SCD-Related Pain Crises in Subgroups of the SUSTAIN Trial, Median (IQR)[36,89]

	Crizanlizumab	Placebo	Hazard Ratio (95% CI)
Annual Rate of Acute Pain Crises, Median IQR			
Concomitant hydroxyurea	2.43 (0.00-4.01)	3.58 (1.13-6.23)	NA
No concomitant hydroxyurea	1.00 (0.00-2.00)	2.00 (1.63-3.90)	NA
2-4 SCD pain crises in previous 12 months	1.14 (0.00-2.00)	2.00 (1.00-3.90)	NA
5-10 SCD pain crises in previous 12 months	1.97 (0.00-3.98)	5.32 (2.01-11.05)	NA
HbSS genotype	1.97 (0.00-3.96)	3.01 (1.01-6.00)	NA
Other genotype	0.99 (0.00-4.01)	2.00 (1.86-5.00)	NA
Time to first on-Treatment Acute Pain Crisis, Median months (IQR)			
Concomitant hydroxyurea	2.43 (1.15-NR)	1.15 (0.33-4.90)	0.58 (0.35-0.96)
No concomitant hydroxyurea	5.68 (3.09-NR)	2.86 (0.79-4.53)	0.39 (0.20-0.76)
2-4 acute pain crises in previous 12 months	4.76 (1.81-NR)	1.61 (0.62-6.70)	0.53 (0.31-0.90)
5-10 acute pain crises in previous 12 months	2.43 (1.25-7.75)	1.03 (0.30-2.97)	0.47 (0.25-0.89)
HbSS genotype	4.07 (1.31-NR)	1.12 (0.33-4.17)	0.50 (0.31-0.80)
Other genotype	6.90 (1.41-NR)	3.09 (1.12-6.21)	0.47 (0.21-1.05)

CI: confidence interval, IQR: interquartile range, NA: not applicable, SCD: sickle cell disease

Harms of Crizanlizumab

There were three deaths among patients treated with crizanlizumab, although none were considered by the investigator to be related to the study therapy. The rate of discontinuation due to an AE was low. The most commonly reported AEs included back pain, nausea, arthralgia, and pyrexia. The prescribing information for crizanlizumab includes warnings for infusion-related reactions and interference with automated platelet counts (i.e., platelet clumping).

There were three deaths among patients treated with crizanlizumab in the SUSTAIN trial.[36] These deaths included 2 patients in the high-dose crizanlizumab group (1 from ACS and 1 from endocarditis and sepsis) and 1 in the low-dose crizanlizumab group (from ACS, aspiration, respiratory failure, and progressive vascular congestion). None of these deaths were considered related to crizanlizumab.

Serious adverse events (SAEs) that occurred in at least 2 crizanlizumab-treated patients included pyrexia (3%) and influenza (5%). In addition, there was one life-threatening case of anemia and one intracranial hemorrhage reported in the low-dose crizanlizumab group. Fewer patients discontinued treatment due to an AE in the crizanlizumab groups (2%) than the placebo group (5%). AEs that occurred in at least 10% of patients treated with high-dose crizanlizumab are reported in Table 4.5.

Table 4.5. AEs in the SUSTAIN Trial of Crizanlizumab[36]

	High-Dose Crizanlizumab (n=66) n, (%)	Placebo (n=62) n, (%)
Headache	11 (17)	10 (16)
Back pain	10 (15)	7 (11)
Nausea	12 (18)	7 (11)
Arthralgia	12 (18)	5 (8)
Pain in extremity	11 (17)	10 (16)
Urinary tract infection	9 (14)	7 (11)
Upper respiratory tract infection	7 (11)	6 (10)
Pyrexia	7 (11)	4 (6)
Diarrhea	7 (11)	2 (3)
Musculoskeletal pain	8 (12)	6 (10)
Pruritus	5 (8)	3 (5)
Vomiting	5 (8)	3 (5)
Chest pain	1 (2)	1 (2)

The prescribing information for crizanlizumab includes warnings for infusion-related reactions and interference with automated platelet counts (i.e., platelet clumping). The FDA is requiring several postmarketing studies, including a clinical trial, to assess the risk of infusion-related reactions and immunogenicity, bleeding complications, and infections. Antibodies against crizanlizumab were not detected during the SUSTAIN trial.

Key Studies of Voxelotor

Evidence on voxelotor was derived from the HOPE trial.[37] This study was a Phase III, placebo-controlled trial that randomized 274 individuals with SCD to receive a once-daily oral dose of 1500 mg of voxelotor (n=90), 900 mg of voxelotor (n=92), or placebo (n=92).

The trial included a screening period of 28-35 days, a treatment period up to 72 weeks, and an end-of-trial visit 3-5 weeks subsequent to the last dose of the trial regimen.[37] As voxelotor was approved at the higher dose (1500 mg), efficacy data pertaining to the low-dose arm of HOPE were not summarized in this review. We supplemented our safety review with data from the low-dose arm.

Patients 12-65 years of age were eligible to participate in the HOPE trial if they had any genotype of SCD, a hemoglobin level between 5.5 and 10.5 g per deciliter (g/dL) during screening, and experienced 1-10 SCD-related acute pain crises in the 12 months prior to enrollment.[37] Patients who had been receiving hydroxyurea at a stable dose for at least three months prior to enrollment were permitted to continue therapy during the trial. Patients were excluded if they were receiving

chronic red-cell transfusions, had received a transfusion in the past 60 days, or had been hospitalized for an SCD-related acute pain crisis within 14 days of providing informed consent.

At baseline, patient characteristics were generally comparable across intervention arms, although there were some imbalances in the SCD genotypes assigned to each group (e.g., 68% of the voxelotor group had the HbSS genotype compared to 80% of the placebo group). Patients in the voxelotor group had a median age of 24 years and were made up of 64% females; 66% of the trial population were black, 68% had an HbSS SCD genotype, and 64% were receiving concomitant therapy with hydroxyurea.[37] The proportion of patients with 1 versus 2-10 SCD-related crises in the previous year, was 39% and 61%, respectively (Table 4.6).

Table 4.6. Key Trial of Voxelotor: HOPE[37]

Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
1. Voxelotor (1500 mg QD, N=90) **2. Voxelotor** (900 mg QD, N=92)‡ **3. Placebo** (N=92)	12-65 years of age SCD diagnosis regardless of genotype 1-10 acute pain crises in past 12 months Hb level between 5.5 and 10.5 g/dL	52-weeks End-of-trial visit 4 weeks after last dose of trial drug or placebo **Early discontinuation** Voxelotor: 27% Placebo: 21%	**Median age:** 24 years (range 12-59) **Black**: 66% **HbSS**: 68% **HbSC**: 3% **HbSβ0**: 20% **HbSβ+**: 8% **Other**: 1% **Hydroxyurea use:** 64% **Acute pain crises in prior 12 months**: 1: 39%, 2-10: 61%	Percentage of participants with Hb response Hb response was defined as an increase from baseline of more than 1.0 g per deciliter at week 24

G: gram, g/dL: grams per deciliter, Hb: hemoglobin, SCD: sickle cell disease

*Baseline Characteristics reported from voxelotor 1500 mg Arm. Baseline characteristics were balanced across treatment arms; ‡ evidence pertaining to efficacy of low-dose voxelotor was not summarized in this report. Safety data from low-dose voxelotor were included in our review of potential harms.

The HOPE trial's primary endpoint was the proportion of patients who had a hemoglobin response, which was defined as an increase from baseline in hemoglobin of more than 1.0 g/dL at week 24.[37] The annualized rate of SCD-related acute pain crises was evaluated as a secondary endpoint. The trial's definition of SCD-related acute pain crises was a composite of ACS and/or moderate to severe pain lasting at least 2 hours with no explanation other than a vaso-occlusive event. The crises must have required oral or parenteral opioids, ketorolac, or other analgesics and have been documented in a medical record that the patient was seen or contacted a physician within one business day of the event.

Clinical Benefits of Voxelotor

Compared to optimal usual care alone (i.e., placebo), voxelotor increased hemoglobin levels and reduced markers of hemolysis. Red-cell transfusions were administered to a greater proportion of voxelotor-treated patients, although statistical testing was not reported. Voxelotor did not significantly reduce the number of acute pain crises and did not improve quality of life as measured by the study. We did not identify any data related to health care utilization for voxelotor.

Effect on Hemoglobin

The HOPE trial's primary endpoint was hemoglobin response, defined as a 1 g/dL change in hemoglobin.[37] At week 24, 51% of the voxelotor group and 7% of the placebo group (p<0.001) had a response; sensitivity analyses accounting for missing data demonstrated consistent results.[92] Improvements in hemoglobin were observed as early as two weeks of follow-up. At week 24, the adjusted mean change in hemoglobin from baseline was 1.1 g/dL (95% CI 0.9 to 1.4) in the voxelotor group and -0.1 g/dL (95% CI -0.3 to 0.2; p<0.001; Table 4.7).[37]

Subgroup Analyses

A greater proportion of patients with a hemoglobin response was observed with voxelotor in subgroups defined by age, use of concurrent hydroxyurea, and baseline hemoglobin level (Table 4.8).[37] The mean change in hemoglobin from baseline to Week 24 in patients treated with voxelotor ranged from 1.0 g/dL to 1.5 across subgroups with and without hydroxyurea use and anemia severity subgroups; hemoglobin levels remained relatively stable in subgroups treated with placebo. Interaction tests to assess whether treatment efficacy differed between subgroups were not reported.

Table 4.7. Hemoglobin Response in Subgroups of the HOPE Trial[37]

	Mean Change in Hemoglobin from Baseline to Week 24, g/dL (95% CI)‡		Difference in Hemoglobin Response Rates at Week 24, % (95% CI)*
	Voxelotor	Placebo	
Age 12-17 years	NR	NR	51.3 (23.0 to 79.5)
Age ≥18 years	NR	NR	43.3 (30.7 to 56.0)
1 prior acute pain crisis in prior 12 months	NR	NR	55.2 (37.1 to 73.2)
2-10 acute pain crises in prior 12 months	NR	NR	37.9 (22.8 to 53.0)
No hydroxyurea use	1.2 (0.8 to 1.7)	0 (-0.3 to 0.3)	34.9 (15.3 to 54.6)
Baseline hydroxyurea use	1.0 (0.7 to 1.4)	-0.1 (-0.3 to 0.1)	50.0 (36.0 to 64.0)
Baseline hemoglobin <7 g/dL	1.5 (0.6 to 2.4)	0.2 (-0.2 to 0.6)	42.9 (-2.0 to 87.8)
Baseline hemoglobin ≥7 g/dL	1.1 (0.8 to 1.4)	-0.1 (-0.3 to 0.1)	44.7 (32.7 to 56.6)

CI: confidence interval, g/dL: grams per deciliter, SCD: sickle cell disease

‡Per protocol analysis with observed data, *ITT analysis: Difference in response rates: voxelotor 1500 mg minus placebo

Markers of Hemolysis

Patients in the voxelotor group had significantly greater reductions from baseline in indirect bilirubin levels and percentage of reticulocytes (Table 4.8).[37] Other laboratory parameters, including absolute reticulocyte count and lactate dehydrogenase level, were not statistically different between groups at week 24. Red-cell transfusions during the trial period were administered to 33% of voxelotor patients and 25% of placebo patients (statistical testing not reported); the majority of these transfusions were due to acute pain crises.[37]

Table 4.8. Change in Hemoglobin and Markers of Hemolysis in the HOPE Trial[37]

	Voxelotor	Placebo	p-value
Primary Endpoint			
Hemoglobin response, n (%)*	46 (51)	6 (7)	p<0.001
LS Mean change from Baseline (95% CI) to Week 24 in Markers of Hemolysis			
Absolute change in hemoglobin level, g/dL	1.1 (0.9 to 1.4)	-0.1 (-0.3 to 0.2)	p<0.001
Relative change in indirect bilirubin level, %	-29.1 (-35.9 to -22.2)	-3.2 (-10.1 to 3.8)	p<0.001
Relative change in percentage of reticulocytes, %	-19.9 (-29.0 to -10.9)	4.5 (-4.5 to 13.6)	p<0.001
Relative change in absolute reticulocyte count, %	-8.0 (-18.1 to 2.1)	3.1 (-7.0 to 13.2)	NS
Relative change in lactate dehydrogenase level, %	-4.5 (-11.9 to 2.8)	-3.4 (-4.0 to 10.9)	NS

CI: confidence interval, g/dL: grams per deciliter, LS: least squares, NS: not significant, *hemoglobin response was defined as a 1 g/dL change in hemoglobin

Acute Complications of SCD

The annualized incidence rate of SCD-related acute pain crisis was evaluated as a secondary endpoint in the HOPE trial and did not differ among trial arms.[37] In the voxelotor group, there were

2.77 (95% CI 2.15 to 3.57) crises per person-year versus 3.19 (95% CI 2.50 to 4.07) in the placebo group (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); 67% and 69% of patients in the voxelotor and placebo arms, respectively, had at least 1 crisis. Investigators noted that a longer duration of follow-up may be required to evaluate the effect of voxelotor on the incidence of acute pain crises. A final analysis will be performed when all subjects complete 72 weeks of treatment or their final study visit.

Sickle cell anemia with crisis, ACS, pneumonia, priapism, and osteonecrosis were recorded as SCD-related treatment-emergent adverse events (TEAEs) in the HOPE trial.[37] Collectively, these events occurred in 76% of voxelotor-treated patients and 73% of placebo-treated patients.[37]

Hospitalization

Although the rate and duration of hospitalizations for SCD-related acute pain crisis were originally defined as outcomes of interest in the HOPE trial's protocol, a protocol amendment in January of 2019 removed it from consideration.[37]

Quality of Life

The HOPE trial assessed the Sickle Cell Disease Severity measure (SCDSM) total symptom score and EuroQOL 5-dimension 5-level (EQ-5D-5L) as exploratory endpoints; no differences were observed between the voxelotor and placebo groups for either outcome.[37,92] Investigators also collected data related to rate of opioid use and school and work attendance, however no results were identified in the public domain.

Harms of Voxelotor

Rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial of voxelotor. The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache. The FDA prescribing information for voxelotor includes warnings for hypersensitivity reactions and interference with laboratory tests.

There were four fatal AEs in the HOPE trial, two of which occurred in patients treated with voxelotor (one from pulmonary sepsis, sickle cell anemia with crisis and acute sickle hepatic crisis; the second from sickle cell anemia with crisis); none of the deaths were determined to be related to the trial drug.[37]

Serious TEAEs that were deemed related to treatment were reported in 3% of patients treated with voxelotor and 1% of placebo-treated patients; 9% of patients in the voxelotor groups discontinued therapy due to a TEAE compared to 4% of patients in the placebo group. The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache (Table 4.9).[37] The FDA

prescribing information for voxelotor includes warnings for hypersensitivity reactions and interference with laboratory tests for quantification of hemoglobin species.

Table 4.9. Treatment-Emergent Adverse Events in the HOPE Trial of Voxelotor[37]

	Voxelotor, n (%)	Placebo, n (%)
TEAE leading to discontinuation	8 (9.1)	4 (4.4)
Treatment-related serious TEAE	3 (3.4)	1 (1.1)
Treatment-related TEAE	34 (38.6)	23 (25.3)
Diarrhea	11 (12.5)	3 (3.3)
Nausea	6 (6.8)	5 (5.5)
Abdominal pain	6 (6.8)	1 (1.1)
Rash	7 (8.0)	4 (4.4)
Headache	5 (5.7)	3 (3.3)
Abdominal pain upper	2 (2.3)	2 (2.2)
Fatigue	0 (0)	0 (0)

SCD: sickle cell disease, TEAE: treatment-emergent adverse event
Table excludes SCD-related adverse events, defined as sickle cell anemia with crisis, acute chest syndrome, pneumonia, priapism, and osteonecrosis

Key Studies of L-Glutamine

The primary source of evidence for our review of L-glutamine was the Phase III, placebo-controlled trial from Niihara et al. (2018);[9] a similarly designed Phase II proof-of-concept study also informed our review, although due to a large rate of trial discontinuation and imbalance in baseline characteristics, evidence from this latter study was considered low quality.[90]

Both studies randomized patients with SCD to receive a twice-daily dose of L-glutamine (0.3 g per kilogram up to 30 g per day) or placebo.[9,90] The trials included a 48-week treatment phase, followed by a 3-week tapering period and 2-week observation period. Patients ≥5 years of age with a diagnosis of HbSS or Hbβ0-thalassemia were eligible to participate if they experienced at least two acute pain crises in the previous year (Table 4.10). Patients who had been receiving hydroxyurea at a stable dose for at least three months prior to enrollment were permitted to continue therapy during the trial. Patients were excluded if they had been hospitalized within two months of screening for something unrelated to SCD, had a prothrombin time international normalized ratio higher than 2, a serum albumin level less than 3.0 g/dL, had received any blood products three weeks prior to screening or L-glutamine within 30 days of screening, or had clinically significant renal or liver disease.

In the Phase III study, randomization was stratified by study site and baseline hydroxyurea use; characteristics were comparable across intervention arms at baseline.[9] Patients in the L-glutamine group had a median age of 19 years and were made up of 52% females; 95% of the trial population

was black, 90% had a diagnosis of sickle cell anemia, two thirds were receiving concomitant hydroxyurea, and 84% had experienced 2-5 acute pain crises in the year prior to enrollment.

Conversely, the Phase II study did not stratify randomization by hydroxyurea use and there were several imbalances in patient characteristics present at baseline; most notably, the Phase II trial differed at baseline with respect to the proportion of females in each group (67% in the L-glutamine group versus 35% in the placebo group), and hydroxyurea use (57% in the L-glutamine-treated group versus 39% in the placebo group.[90]

Table 4.10. Key Trials of L-Glutamine[9,38,90]

Trial	Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
Phase III[9]	1. **L-glutamine** (0.3 g/kg, N=152) 2. **Placebo** (N=78)	• ≥ 5 years old age • SCD diagnosis (homozygous hemoglobin S [HbSS], or sickle cell thalassemia (HbSβ⁰-thalassemia) • ≥2 acute pain crises documented in previous year	52-weeks 3-week tapering period followed by 2-week observation after 48 weeks **Early discontinuation** L-glutamine: 36% Placebo: 24%	**Median age**: 19 years (range 5-57) **Black**: 95% **HbSS**: 90% **HbSC**: NR **HbSβ⁰**: 10% **HbSβ⁺**: 2% **Other**: NR **Hydroxyurea use**: 66% **Acute pain crises in prior 12 months**: 0-1: 0.7%, 2-5: 84%, 6-9: 10%, ≥ 10: 5%	**Number of acute pain crises through week 48:** Pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) or outpatient treatment center or during hospitalization. Acute chest syndrome, priapism, and splenic sequestration were classified as sickle cell–related events regardless of the need for narcotics or ketorolac.
Phase II[90]	1. **L-glutamine** (0.3 g/kg N=37) 2. **Placebo** (N=33)	• ≥ 5 years old age • SCD diagnosis (homozygous hemoglobin S [HbSS], or sickle cell thalassemia (HbSβ⁰-thalassemia) • ≥2 acute pain crises in previous year	52-weeks 3-week tapering period followed by 2-week observation after 48 weeks **Early discontinuation** L-glutamine: 51% Placebo: 64%	**Median age**: 29 (range 13-58) **Black**: 97% **HbSS**: 94% **HbSC**: NR **HbSβ⁰**: 7%** **HbSβ⁺**: 7%** **Other**: NR **Hydroxyurea use**: 57%	**Number of acute pain crises through week 48:** A visit to a medical facility lasting >4 hours for acute sickling-related pain that was treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used).

*Baseline Characteristics reported from L-Glutamine 0.3k/kg arm. Baseline characteristics were balanced across treatment arms,**: reported as beta thalassemia

The primary endpoint in both trials of L-glutamine was the number of acute pain crises through week 48 (Table 4.10). In the Phase III study, an acute pain crisis was defined as pain that led to treatment with a parenterally-administered narcotic or ketorolac in a medical facility.[9] ACS, priapism, and splenic sequestration were considered acute pain crises, irrespective of the need for narcotics or ketorolac. The Phase II study's definition required that the visit to the medical facility last more than four hours and permitted treatment with oral narcotics in facilities where that was the only formulation in utilization; ACS, priapism, and hepatic or splenic sequestration were considered acute pain crises.[90]

There was a high and differential rate of dropout across treatment groups in both studies. More than half of the Phase II participants withdrew from the trial early (51% and 64% in the L-glutamine and placebo arms, respectively), and about a third of participants in the Phase III trial discontinued prior to completing 48 weeks (36% of the L-glutamine arm and 24% of the placebo arm).[9,90] The most commonly cited reasons for discontinuation included withdrawal of consent and nonadherence.

Two additional Phase II studies were identified in our review of the FDA clinical review packet for L-glutamine and the clinicaltrials.gov site that would have matched our PICOTS criteria for inclusion but have not been published. One of these studies was terminated early because it did not reach the targeted enrollment of 50 participants; the other study had insufficient data for the primary endpoint analysis due to a high rate of discontinuation (6 out of 24 patients completed the trial). We have summarized the limited information we have for these two studies in Appendix Table D18.

Clinical Benefits of L-Glutamine

Compared to optimal usual care alone (i.e., placebo), treatment with L-glutamine appeared to reduce the number of acute pain crises and hospitalizations, although the magnitude of benefit is uncertain. Due to a large and differential rate of withdrawal from the Phase II and Phase III studies of L-glutamine, investigators relied on imputation methods to calculate the rate of crises. These results were sensitive to the applied assumptions and were not statistically significant under certain approaches. We did not identify any data related to quality of life for L-glutamine.

Acute Complications of SCD

Both the Phase II and Phase III studies of L-glutamine evaluated the number of SCD-related acute pain crises through Week 48 as a primary endpoint, although each study defined a pain crisis slightly differently (see Table 4.10.). The Phase II study did not meet the prespecified significance level for this analysis.[90] Statistically significant differences in the number of SCD-related acute pain crises were reported in the Phase III trial, with a median count of 3.0 in the L-glutamine group and 4.0 in the placebo group (p=0.005).[9] Interim analyses at 24 weeks did not reach specified significance levels (p=0.005) in either study.[38]

Due to the high and differential rate of trial discontinuation prior to the completion of the 48-week treatment period, investigators in the Phase III study imputed the crisis results.[9,38] The investigators assigned a crisis count to patients who dropped out of the study that was derived from the rounded group average for patients who completed the 48-week treatment period. A count of 3 was assigned to patients in the L-glutamine arm who dropped out of the study early who experienced fewer than 3 crises and a count of 4 was assigned to placebo patients who dropped out early having experienced fewer than 4 crises. Patients who dropped out of the study early with more than these averages were included with the count at the time of dropout carried forward through 48 weeks.

This method may have introduced bias in the results because the high number of non-completers meant that the large proportion of imputed counts may have changed the distribution of data. Moreover, the FDA was concerned that the imputation method did not control for variables that could modify the outcome, such as time spent on study, or study stratification factors (i.e., region of participating site and hydroxyurea use).[38]

The FDA conducted several sensitivity analyses using different assumptions about the dropout data. Their analyses suggested that the reduction in crises from L-glutamine versus placebo ranged from 0.4 to 0.9.[38] Consequently, FDA concluded that the results of the sensitivity analyses show a "modest trend supporting a claim of benefit for [L-glutamine]", but noted that in some analyses, the upper limits of the confidence intervals for rate ratios comparing the treatment groups included 1.[38]

To circumvent the difficulties presented by imputation of incomplete crisis counts, the FDA also conducted a recurrent event analysis of acute pain crises that censored patients with no recorded events at their last visit. The analysis calculated a hazard ratio of 0.73 (95% CI: [0.55, 0.99]), and estimated 3.0 versus 3.8 acute pain crises at 48 weeks in the L-glutamine and placebo arms, respectively.

Table 4.11. Rates of Sickle Cell Crisis through Week 48 using Different Analysis Assumptions in the Phase III Trial of L-Glutamine[9,38]

Analysis set	L-Glutamine (n=132) Median (range)	Placebo (n=74) Median (range)	Rate Ratio (95% CI)
Investigator's imputation method	3 (0 to 15)	4 (0 to 15)	NR
Sensitivity analyses from FDA using Negative binomial Regression			
FDA sensitivity analysis: excludes non-completers with zero crises recorded (n=206)	3.3 (2.8 to 3.8)	4.1 (3.3 to 4.9)	0.80 (0.64 to 1.01)
ITT population assuming crisis count for non-completers with zero crises recorded was 0 (n=230)	3.3 (2.7 to 3.9)	4.2 (3.4 to 5.1)	0.77 (0.61 to 0.99)
Multiple imputation for crisis counts in non-completers with zero crises recorded, using information on treatment group, study stratification factors, time on study, baseline age, and baseline crisis count	3.9 (3.3 to 4.5)	4.3 (3.2 to 5.4)	0.91 (0.73 to 1.12)
Recurrent event analysis from FDA			
Recurrent event analysis based on the proportional rate regression model	3.0 (2.5 to 3.4)	3.8 (3.1 to 4.5)	Hazard ratio 0.73 (0.55 to 0.99)

All FDA analyses take time on study into account and control for study stratification factors (region of study site and baseline hydroxyurea use)

CI: confidence interval, NR: not reported, ITT: intention to treat

The median number of days to first SCD-related acute pain crisis was a post hoc analysis in the Phase III study. The results suggested that L-glutamine delayed the time to first crisis (median 84 days [95% CI 62.0 to 109.0]) compared to placebo (median 54 days [95% CI 31.0 to 73.0]; p-value=0.0152).[9,38] The Phase II study reported a median of 64 days with L-glutamine versus 44 days with placebo (p=0.5861).[38,90]

Another post hoc analysis of the incidence of ACS in the Phase III study suggested a lower incidence among patients treated with L-glutamine (mean 0.1 [SD 0.37] versus 0.3 [SD 0.63] in the L-glutamine and placebo arms, respectively; 8.6% in the L-glutamine group vs. 23.1% in the placebo group experienced one or more episodes of ACS (p=0.003).[9,38] There were only two episodes of ACS in the Phase II study, so no analyses were performed.[38,90]

Hospitalization

At Week 48, the median number of SCD-related hospitalizations in the Phase III trial was lower in the L-glutamine group than the placebo group (p=0.005).[9] The trial also reported fewer days spent in the hospital, but not fewer emergency department visits (Table 4.12.). Statistically significant differences in the mean number of hospitalizations were observed at Week 24 of the Phase II study

(mean [SD] 0.8 [1.2] with L-glutamine vs. 1.3 [1.4] with placebo; p=0.04] but not Week 48. The mean number of emergency room visits did not statistically differ in the Phase II trial.

Table 4.12. Health Care Utilization in Phase III Trial of L-Glutamine through Week 48[9]

	L-Glutamine (n=152)	Placebo (n=78)	p-value
No. of hospitalizations for SCD-related pain, median (range)	2 (0-14)	3 (0-13)	p=0.005
No. of ED visits for SCD-related pain, median (range)	1 (0-12)	1 (0-15)	p=0.09
Cumulative no. of days in hospital, median (range)	6.5 (0-94)	11 (0-187)	p=0.02

ED: emergency department, No.: number, SCD: sickle cell disease

Quality of Life

The Phase II trial of L-glutamine planned to evaluate pediatric quality of life as an exploratory endpoint but did not perform any analyses due to the small number of pediatric patients who were enrolled.[38,90] The Phase III trial did not assess quality of life.

Markers of Hemolysis

No significant differences were observed between groups in changes in hemoglobin, hematocrit level, or reticulocyte count in the Phase III trial of L-glutamine.[9]

Subgroup Analyses

The Phase III trial of L-glutamine performed subgroup analyses of the rate of SCD-related acute pain crises in patient groups defined by hydroxyurea use at baseline, sex, and age.[9] Due to the high level of early withdrawal from the study, and resulting uncertainties surrounding the imputation methods employed by study investigators, the FDA also analyzed the data from these subgroups by excluding the non-completers.[38] Results from both analyses are reported in Table 4.13. Overall, L-glutamine appeared to have a consistent treatment benefit across subgroups, although the rate of crises in pediatric patients (age ≤18) seemed to be similar in both treatment arms (estimated 3.3 vs 3.5 crises in the L-glutamine and placebo arms respectively).[38] A similar trend was observed in patients who received a lower dosage (analyzed by the FDA only) due to a lower body weight. Nevertheless, interaction tests to assess whether treatment efficacy differed between subgroups were not significant.

Table 4.13. Subgroup Analyses of Rate of Acute Pain Crises through 48 Weeks in the Phase III Trial of L-Glutamine

	Niihara 2018[9]		FDA[38]	
	Rate Ratio	95% CI	Rate Ratio	95% CI
Hydroxyurea Use at Baseline	0.77	NR	0.79	(0.59 to 1.06)
No Hydroxyurea Use at Baseline	0.78	NR	0.83	(0.58 to 1.21)
Male	0.73	NR	0.71	(0.50 to 1.02)
Female	0.81	NR	0.86	(0.63 to 1.17)
Age ≤18	0.93	NR	0.95	(0.69 to 1.29)
Age >18	0.64	NR	0.67	(0.48 to 0.94)
Dose <30 g/day	NR	NR	0.90	(0.66 to 1.22)
Dose 30 g/day	NR	NR	0.58	(0.43 to 0.79)
2 acute pain crises in prior year	0.87	(0.58 to 1.33)	NR	NR
3-5 acute pain crises in prior year	0.74	(0.53 to 1.04)	NR	NR
≥6 acute pain crises in prior year	0.82	(0.50 to 1.34)	NR	NR

FDA: Food and Drug Administration, CI: confidence interval, NR: not reported

Harms of L-Glutamine

The majority of SAEs observed with L-glutamine were considered to be unrelated to study treatment. A greater proportion of patients treated with L-glutamine experienced gastrointestinal disorders (constipation, nausea, vomiting), headache, pain in extremities, back pain, and noncardiac chest pain. Treatment discontinuation resulting from AEs was low with L-glutamine.

A total of three treatment-emergent deaths occurred in patients treated with L-glutamine during the Phase II and Phase III trials from sudden cardiac death and/or multiorgan failure.[9,38,90] These patients had a history of organ failure and comorbidities and the investigator did not determine the deaths to be related to the study drug. The FDA concluded that the role of L-glutamine in these deaths was unlikely but in the absence of autopsy findings, there was insufficient data available to be able to categorically rule it out.[38] FDA reviewers noted that the mortality rate observed in other clinical studies of patients with SCD was like that observed in the L-glutamine trials. However, the safety data on L-glutamine from trials in other conditions provides less reassurance. The REDOXS trial of critically ill patients with multiorgan failure reported that patients treated with higher doses and different formulations of L-glutamine than indicated in SCD (approximately 0.35 g/kg/day of IV glutamine according to ideal body weight and 30 g/day of enteral glutamine) had significantly higher in-hospital mortality and mortality at 6 months than patients who did not receive L-glutamine.[93]

In the Phase III trial, SAEs occurred in 78% of patients treated with L-glutamine versus 87% of placebo-treated patients.[9] The most common SAEs in the L-glutamine arm were considered to be

related to SCD rather than treatment; these included sickle cell anemia with crisis (66%), ACS (7%), and pneumonia (5%).[38] TEAEs that were considered by investigators to be related to study drug occurred in 19% of patients treated with L-glutamine and 14% of patients treated with placebo.[38] SAEs that were deemed to be related to L-glutamine included hypersplenism (n=1), sickle cell anemia with crisis (n=1), abdominal pain (n=1), and chest pain (n=1).[38]

Discontinuation due to TEAEs was reported in 3% of the L-glutamine group and 1% of the placebo group. The most commonly reported AEs included gastrointestinal disorders (constipation, nausea, vomiting), headache, pain in extremity, back pain, and noncardiac chest pain (Table 4.14).

Table 4.14. AEs that occurred during the Phase III Trial of L-Glutamine[9]

	L-Glutamine (n=151) N (%)	Placebo (n=78) N (%)
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Abdominal pain upper	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
Chest pain (noncardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Urinary tract infection	10 (6.6)	3 (3.8)
Pain in extremity	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Nasal congestion	11 (7.3)	5 (6.4)
Tachycardia	8 (5.3)	4 (5.1)

Uncertainty and Controversies

Generalizability of Patient Populations Studied

Because there are so few therapies available for patients with SCD, there may be a tendency to prescribe these three new therapies to similar patient populations. However, there are important patient subpopulations with SCD that may have different responses to each of the three therapies.

Although patients with SCD may experience their first acute pain crisis or other important clinical manifestation before their first birthday, very few children, and no infants were included in these studies. The youngest ages included in the available studies were 16 years for crizanlizumab, 12 years for voxelotor, and 5 years for L-glutamine. These inclusion criteria make it difficult to generalize results to pediatric patients with SCD, all of whom will likely experience anemia and/or

pain. There are several ongoing trials of crizanlizumab and voxelotor (Appendix C), which are enrolling patients as young as 2 years of age. These trials should help fill in some of the current knowledge gaps about the efficacy and safety of these agents in pediatric patients.

Patients in these trials differed by factors other than age. Most patients in the studies were homozygous for hemoglobin S, though a minority of patients with other genotypes such as hemoglobin Sβ^0 or Sβ$^+$ thalassemia, hemoglobin SC, and other variants were included. None of the trials reported details about subphenotypes. Because the majority of patients enrolled in the trials had genotype HbSS, there are insufficient data available to determine whether the risk/benefit profile of these therapies differs across genotypic and phenotypic subpopulations.

The definition of acute pain crisis, baseline hemoglobin levels, and baseline number of pain crises also differed across studies. Additionally, some of the studies excluded patients who were receiving chronic pRBC transfusions.   Each of these factors could impact the results of the studies and are clinically relevant as clinicians make prescribing decisions for individual patients.

Generalizability of Results Based on "Optimal Usual Care" Control Arms

It is evident from input from clinical experts and patient advocates that the quality and intensity of "usual care" delivered to patients in the control arms of the clinical trials we reviewed was far better than the usual care received by the vast majority of patients with SCD in the US. For example, approximately 63% of patients in the RCT of crizanlizumab received hydroxyurea, whereas our best estimates of real-world usual care suggest that at most 15% are likely to receive this drug.[94] The level of attention given to hydration, oxygenation, transfusion needs, and other clinical aspects of care was likely far higher than the norm in real-world practice. This is the primary reason we have labeled the "usual care" arm from the clinical trials as "optimal usual care."

How this difference in "usual care" affects the magnitude of the relative benefits of treatment with these new interventions is difficult to judge. It is difficult to know whether the magnitude of benefit would be greater in a real-world clinical setting where usual care has not been maximized or whether maximizing baseline care is a prerequisite for maximizing the benefits of these new therapies. What is certain, however, is that the introduction of new, effective treatments for SCD serves as an opportunity for the overall care of patients with SCD to be re-imagined and improved from top to bottom.

Quality of Life

None of the trials demonstrated an improvement in quality of life based on the instruments chosen by the investigators and studies for L-glutamine did not include any measures of quality of life. This is an especially important consideration in SCD as patients and caregivers have repeatedly reported on the devastating impact of pain on their QOL. It is unclear if this finding is due to the instruments used in the trials or if these new therapies provide some benefit to patients but not at a level that

improves their quality of life. The BPI, SF-36, and EQ-5D-5L are all general quality of life instruments that are used across a number of different health conditions and were used in studies of both crizanlizumab and voxelotor. It is possible that instruments not designed to assess quality of life in a specific disease state are not sensitive enough to detect important changes in patients with SCD. The HOPE trial for voxelotor also used the Sickle Cell Disease Severity Measure (SCDSM), an SCD specific instrument. This instrument was not able to detect an improvement in quality of life in the HOPE trial. For historic context treatment with hydroxyurea has been shown to both decrease pain crises and improve quality of life. The PedsQL 4.0 used in pediatric patients with SCD and the Profile of Mood States, SF-36, and the Ladder of Life, used in adult patients with SCD were able to detect improved quality of life associated with decreased pain crises in patients treated with hydroxyurea.[95,96] It would be anticipated that decreasing pain crises would increase quality of life so there continues to be important uncertainty about whether these new therapies impact quality of life or whether the instruments used in the clinical trials were not sufficiently sensitive to detect that improvement.

Drop Out

All studies reviewed had significant rates of attrition. If drop-out rates in real-world practice are even higher than those seen in the clinical trials, which is likely, it is possible that the magnitude of longer-term benefits seen with treatment in the studies would not be realized. Some clinical experts also expressed concern that sudden withdrawal or noncompliance with voxelotor might result in a high rate of hemolysis, potentially worsening vasculopathy. Other experts reported relatively poor compliance with L-glutamine in some of their patients due to the dosing regimen. There is currently no information on how to safely discontinue any of these medications should that be necessary.

Durability of Benefits

At this time there is no data on the durability of the effects observed in the clinical trials. We do not know if positive effects will continue to be seen in patients over the course of several years or a lifetime.

Long-Term Safety

All three therapies are relatively new, each with a novel mechanism of action. We lack long-term safety data and it is possible that undetected safety events will be identified over time or that the benefit/risk profile might change over time. There is also uncertainty as to which subpopulations of patients may have an increased risk of AEs. For example, some clinical experts expressed concern about a potential risk of hyperviscosity in patients with relatively high levels of hemoglobin who might be prescribed voxelotor. Other experts were concerned the higher drop out rates in the L-glutamine exposed patients might signal a hidden safety problem.

Combination Therapy

From a clinical perspective these therapies might be used in various combinations with hydroxyurea, chronic transfusion, and each other as they all have different mechanisms of action. Without data to help clinicians understand the optimal way to combine therapies, there is uncertainty about whether combination therapy represents an optimal approach for some patients or whether combining therapies will increase AEs (and costs) without commensurate clinical benefit.

Impact of Therapy on Acute and Chronic Outcomes and Mortality

The full clinical benefit of these therapies is unclear. Although acute pain crises have been associated with an increased risk of other acute and chronic conditions, it is not possible to know at this time if treatment with crizanlizumab will decrease the rates of these conditions or will improve overall survival in treated patients. For all three treatments reviewed in this report there are reasons to be optimistic about beneficial long-term effects, and our economic model has made favorable assumptions about the linkage between short-term outcomes and longer-term health benefits. Nevertheless, there remains significant uncertainty about the true magnitude of the benefits that patients will receive.

For patients treated with voxelotor there is an additional concern that adds to the uncertainty about long-term benefits. The trial result demonstrated that although hemoglobin levels increased with treatment, pain crises did not decrease. There was also a numerically higher rate of transfusion in the treated group compared to the placebo group, a puzzling finding given that voxelotor did increase average hemoglobin levels, but one most likely due to a higher rate of pain crises among treated patients. As with crizanlizumab, there are no data on whether treatment with voxelotor will improve acute or chronic complications of SCD or increase survival.

For patients treated with L-glutamine an additional layer of uncertainty is created by the significant differential drop-out rate that saw treated patients dropping out at a higher rate than patients receiving placebo. Furthermore, the impact of L-glutamine on pain crises differed based on the imputation method used to account for those patients who dropped out. As reported in Table 4.11 the investigator's imputation method resulted in a median count of 3 crises in those treated with L-glutamine versus 4 in those treated with placebo. However sensitivity analyses conducted by the FDA systematically adjusting for non-completers, study group, stratification factors, time on study, baseline age, and baseline crisis counts resulted in a median count of 3.9 crises in those treated with L-glutamine and 4.3 in those treated with placebo, with a rate ratio of 0.91 (0.73-1.12). Other imputation methods also conducted by FDA, with fewer adjustment factors resulted in median rates in between the investigator's rates and median rates using all adjustment factors. As with crizanlizumab and voxelotor, there are no data on whether treatment with L-glutamine will improve acute or chronic complications of SCD or increase survival.

4.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 4.1.), we assigned independent evidence ratings for crizanlizumab, voxelotor, and L-glutamine, each compared to optimal usual care as defined by the placebo arm of their respective clinical trials.

Figure 4.1. ICER Evidence Rating Matrix

A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D= "Negative"- High certainty of an inferior net health benefit
B+= "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Any situation in which the level of certainty in the evidence is low

Table 4.15. ICER Evidence Ratings

Intervention	ICER Evidence Rating
Crizanlizumab	B+
Voxelotor	P/I
L-Glutamine	P/I

Crizanlizumab versus Optimal Usual Care

The primary source of evidence for our evaluation of crizanlizumab was a single Phase II trial (SUSTAIN).[36] Compared to optimal usual care, crizanlizumab demonstrated a statistically significant reduction in the rate of acute pain crises in patients with SCD and prolonged the time to first and second crisis. Patients treated with crizanlizumab experienced approximately one fewer pain crisis per year, from approximately 3 in optimal usual care to approximately 2 with treatment.

Although rates of acute pain crises were reduced, statistically significant improvements in the annual rate of days hospitalized and quality of life were not observed in the SUSTAIN trial. Questions about safety also remain. Crizanlizumab was relatively well-tolerated during SUSTAIN's 52-week treatment phase, however risks for long-term adverse outcomes are hard to judge, a problem common to all newly introduced treatments with a new mechanism of action. The FDA is requiring several postmarketing studies, including a clinical trial to assess the risk of infusion-related reactions and immunogenicity, bleeding complications, and infections.

Overall, we judged that the statistically significant reduction in pain crises was enough to give adequate certainty that crizanlizumab will provide a positive net health benefit. However, the difficulty in estimating the amount of longer-term organ system benefit conveyed by the absolute reduction in acute pain crises, coupled with uncertainty about long-term safety, gives us only moderate certainty overall in the magnitude of net health benefit, which seems likely to range from small to substantial, a "B+" rating in the ICER Evidence Matrix.

Voxelotor versus Optimal Usual Care

Compared to optimal usual care alone, voxelotor improved laboratory parameters, including an increase in hemoglobin and reductions in hemolysis markers such as bilirubin and percent reticulocytes. But voxelotor did not significantly reduce the annualized incidence rate of acute pain crises and has not yet demonstrated an effect on quality of life. Annualized incidence rates of acute pain crises were very similar across the voxelotor arms and placebo arms, such that the best suggestion of a trend toward improvement might be an approximate risk reduction of 13% with a confidence interval that crosses one (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); a longer

duration of follow-up will be necessary to determine whether voxelotor improves this important outcome. Although the rate of acute pain crises and quality of life were secondary outcomes, they are important outcomes to patients and linking an increase in hemoglobin levels to these or other patient-important outcomes will be helpful over time. We did not identify any data related to health care utilization for voxelotor that would indicate a reduction in transfusions. Although it seems logical to assume that for some patients there will be reductions in transfusions over time, this has not yet been demonstrated in the clinical evidence.

Does an increase of 1 g/dL of hemoglobin improve short or long-term health outcomes?   We heard from some clinical experts that even an additional 1 g/dL of hemoglobin can reduce patient fatigue and potentially reduce the risks for specific longer-term harms such as high-output congestive heart failure.

Separate from questions about increases in hemoglobin is the extent to which reduction in hemolysis improves short or long-term outcomes. Again, some clinical experts feel there are strong correlational data to support the benefits of reduced hemolysis. For example, several studies have shown higher rates of leg ulcers, priapism, renal dysfunction, stroke and mortality with higher rates of hemolysis and hemolytic byproducts, and there may be broader clinical implications as well.[39] But on the other side of this issue lies the uncertainty of whether there is a threshold of reduced hemolysis required to achieve clinical benefit, and the short-term data available make it impossible to determine the answer to this question.

Safety issues, including rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial. Further study of the long-term safety of voxelotor, however, is required.

Overall, we felt that it was difficult to ascertain the net health benefit of voxelotor with available data at its launch. Nonetheless, we feel that there is less than a 10% chance that treatment will lead to net harm over a broad population. Given that we cannot determine the magnitude of the clinical benefits but feel they are likely to be somewhat greater than usual care, we have assigned a rating of "Promising but Inconclusive" (P/I) to the comparative clinical effectiveness of voxelotor at this time.

L-Glutamine versus Optimal Usual Care

The Phase II and Phase III trials of L-glutamine showed reductions in the number of acute pain crises and hospitalizations, although these results were not robust to different analytic methods needed to account for a large and differential rate of trial withdrawal across treatment arms. This led the FDA to conclude that results trended in favor of L-glutamine but that the magnitude of benefit was uncertain.[38] L-glutamine is considered to have a relatively benign safety profile, with few SAEs in the Phase III trial determined to be related to therapy. Nevertheless, a trial that administered higher doses and different formulations of L-glutamine in critically ill patients (without SCD) with

multiorgan failure found that L-glutamine increased mortality and the FDA could not categorically rule out that the deaths that occurred in the Phase II and III trials in patients with SCD were unrelated to the study drug. Overall, there were problems with the conduct and analyses of the available phase II and phase III trials that lead to uncertainty about the magnitude of clinical benefit as well as some *a priori* safety concerns from the use of L-glutamine in other clinical settings.

We therefore judged that the findings on clinical benefit are too uncertain to allow a clear determination of their magnitude, but it appears most likely that L-glutamine does provide some clinical benefit. However, with residual safety concerns and uncertainty about the clinical benefits due to trial limitations, we feel there remains a small risk that L-glutamine produces net harm overall, but that this risk is less than 10%. In our view, therefore, we rate the evidence on the comparative clinical effectiveness of L-glutamine to be "Promising but Inconclusive" (P/I) within the parameters of the ICER Evidence Matrix.

5. Long-Term Cost Effectiveness

5.1 Overview

The primary aim of this analysis was to estimate the lifetime cost effectiveness of treatments for SCD using a decision analytic model. Crizanlizumab, voxelotor, and L-glutamine, each combined with usual care, were compared to usual care alone. The model estimates outcomes that include life years gained, quality-adjusted life years (QALYs) gained, equal value life years gained (evLYG), clinical events, pain crises avoided, change in hemoglobin, and total costs for each intervention over a lifetime time horizon. The base-case analysis used a health care sector perspective (i.e., direct medical care costs only), with the societal perspective as a co-base case, presented directly alongside the health care sector perspective analysis. Because the societal costs of care for sickle cell disease are large relative to the direct health care costs, and the impact of treatment on these costs is substantial (i.e., there are substantial differences in the cost-effectiveness findings between the two perspectives), the societal perspective is included as a co-base case. In this case, the incremental cost-effectiveness ratio from the two perspectives changes by greater than 20% for two of these drugs and greater than $200,000 per QALY for all three. (See Appendix Table E1 for an inventory of items included in the health care sector and modified societal perspective analyses.) All costs and outcomes were discounted at 3% per year.

This model focuses on improvements in both quality of life and length of life. SCD has a large impact on patients' psychosocial well-being. Many of these impacts are captured in the outcomes and measures of quality of life included in the model. It is important to note that economic models such as this one cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations such as patients with SCD. It is also unclear what impact treatments for these populations will have on those systemic issues, or vice versa. Further improvements from treatments for SCD that may not be captured by the model are discussed in other sections of the report.

The analytic framework for this assessment is depicted in Figure 5.1 below.

Figure 5.1. Model Framework
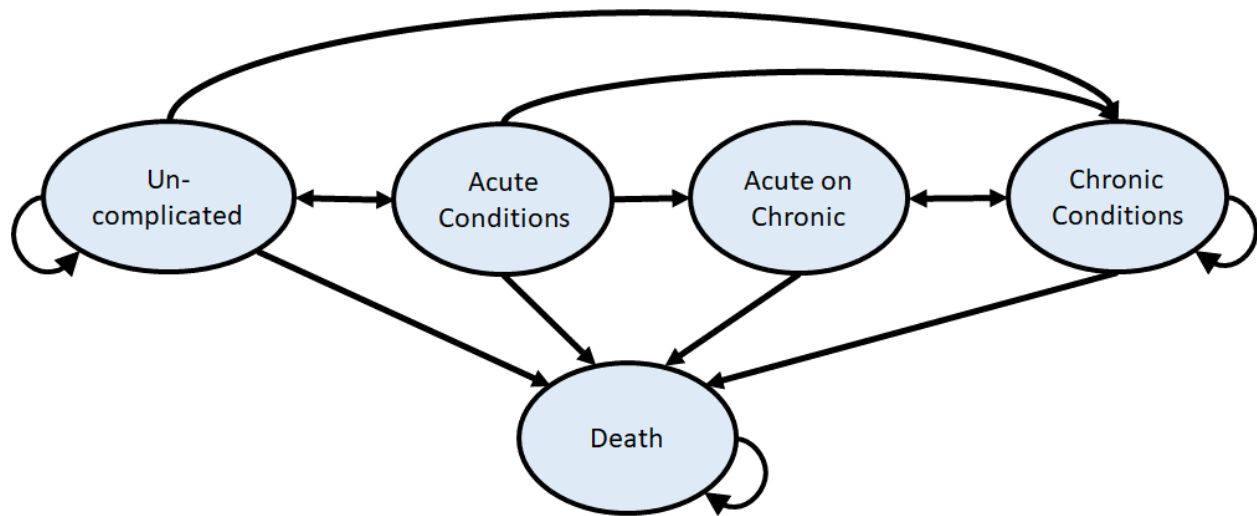
5.2 Methods

We developed a *de novo* decision analytic model for this evaluation, informed by the SUSTAIN trial, HOPE trial, and Niihara et al. 2018, relevant quality of life literature, and other prior economic models. The model was developed in Microsoft Excel for Office MSO (ver. 16.0.11328.20390 64-bit).

Model Structure

The model (Figure 5.1) is a cohort-level, Markov model of costs, quality of life, clinical events, and mortality associated with SCD among children and adults in the US diagnosed with the disease, using a 2-week cycle length. This modeling approach was chosen due to the chronic nature of disease and the multiple re-occurring events in SCD. The model focuses on transitions between acute and chronic health states and includes the risk of death. The acute and chronic conditions considered in the model are listed in Table 5.1. Treatments that delay or avoid acute and chronic conditions will improve patients' health, quality of life, and health care costs. Evidence of treatment effects on acute pain crises and level of hemoglobin come directly from the trials. The model included the impact of these treatment effects on other acute and chronic outcomes. Evidence linking the relationship between acute pain crises and levels of hemoglobin to other acute and chronic conditions come from multiple sources and assumptions (detailed below), as these were not directly measured in the clinical trials. In the model, an acute pain crisis is defined similarly to the trial definitions and includes hepatic sequestration, splenic sequestration, and priapism; acute chest syndrome was modelled separately.

Table 5.1. Acute and Chronic Conditions Included in the Model

Clinical Outcomes	
Ischemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode (including hepatic sequestration, splenic sequestration and priapism)	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Myocardial Infarction	Heart Failure
Acute Kidney Injury/Renal Infarction	Nephropathy, Chronic Kidney Disease
Stroke	Neurocognitive Impairment
Mortality	Mortality
Anemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode (including hepatic sequestration, splenic sequestration and priapism)	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Stroke	Heart Failure
Mortality	Nephropathy, Chronic Kidney Disease
	Neurocognitive Impairment
	Fatigue
	Mortality
	Iron Overload Due to pRBCs

pRBC: packed red blood cells

Target Population

The base-case model uses the average of the median ages reported in the trials, 24 years. This is meant to make the model representative of the population for which there is efficacy data. The proportion of females used in the model was 52%, as this was reported in both the SUSTAIN trial and Niihara et al. 2018. The base-case model evaluated a population with a baseline rate of 3 acute pain crises per year. This was meant to be similar to the placebo arms of the SUSTAIN and HOPE trials that reported 2.98 and 3.19 crises per year. Prevalence of chronic conditions was estimated by using the Markov model to simulate a cohort of patients from birth to the starting age of the analysis. For instance, to estimate the prevalence of each chronic condition at age 24 years, the Markov model was run from birth for 24 years, and the proportion of patients in each chronic condition at 24 years was reported and then used as the starting population in the base-case analysis. Because many patients will have already developed chronic conditions by age 24, we also explored results in scenario analyses for younger populations, beginning treatment at age 5 for the L-glutamine comparison (the indicated starting age for L-glutamine), age 12 for the voxelotor comparison (the indicated starting age for voxelotor) and at age 16 for the crizanlizumab comparison (the indicated starting age for crizanlizumab). We also include subgroup analyses based on frequency of acute pain crises. The demographic and clinical characteristics of the patient

population for our base-case analyses are summarized and compared to those reported in the trials in Table 5.2.

Table 5.2. Base-Case Model Cohort Characteristics

	Model Inputs for Base Case	Standard of Care in SUSTAIN trial[36]	Standard of Care in HOPE trial[37]	Standard of Care in Niihara 2018 trial[9]
Age at enrollment	24	16	12	5
Median age (years)		29	24	19
Female, %	52	52	54	52
Weight (kg)	69.0	69.0	NR	67.1†
Frequency of Acute Pain Crises (mean per year)	3	2.98	3.19	4.3
Prevalence of Chronic Conditions*				
Opioid Tolerant/Dependent (per 1000)	18	NR	NR	NR
Pulmonary Hypertension (per 1000)	342	NR	NR	NR
Heart Failure (per 1000)	130	NR	NR	NR
Chronic Kidney Disease (per 1000)	214	NR	NR	NR
Post-stroke (per 1000)	243	NR	NR	NR
Neurocognitive Impairment alone (per 1000)	63	NR	NR	NR
Fatigue alone (per 1000)	285	NR	NR	NR

NR: not reported

* The model inputs for the prevalence of chronic conditions were calculated using the model. The model was run using the base case annual incidence of each condition and risk factors for each condition as described in the tables below. A cohort starting at an age of 0 years was run through the model and the prevalence of each condition was estimated at each year. The estimate at age 24 years was then used as the starting prevalence for the patients in the cost-effectiveness model.

† Data point taken from FDA Review Packet[38]

Treatment Strategies

The list of treatment strategies was developed during the scoping phase of this report with input from patient organizations, clinicians, manufacturers, and payers, and were chosen to reflect real-world treatment decisions and those in the clinical trials. The list of interventions is presented below:

- Crizanlizumab in addition to usual care
- Voxelotor in addition to usual care
- Pharmaceutical-grade L-glutamine in addition to usual care

In the main analysis each intervention is compared to usual care. Usual care is meant to correspond to the treatment in clinical practice that each of these treatments would be added to in the real world. Treatment effects of the usual care arm in the model are informed by the placebo arm in the trials. The acute and chronic event rates of the usual care arm in the model are informed by real-world evidence. The real-world evidence comes from a population in which 16% received chronic transfusions. This provides an average risk of acute events and chronic conditions for a population on usual care. However, individual risks will vary from the averages used in the model since the care received by many patients in actual practice is also variable.

Doses for each treatment used in the model are shown in Table 5.3. Given that some of the treatments are weight-based, the doses of treatments change over time as the modeled population ages and the average weight increases.

Table 5.3. Treatment Regimen Modeled Dosages

Generic Name	Crizanlizumab	Voxelotor	L-glutamine
Brand Name	Adakveo	Oxbryta	Endari
Manufacturer	Novartis	Global Blood Therapeutics	Emmaus Life Sciences
Route of Administration	Intravenous	Oral	Powder, for oral solution
Dosing	5.0 mg/kg, administered at weeks 0, 2, and then every 4 weeks	1500 mg, once daily	5-15 grams, depending on body weight, twice daily

mg: milligram, kg: kilogram

Key Model Characteristics and Assumptions

Key model assumptions are listed in Table 5.4, along with the rationale for each. In general, where there was uncertainty in the evidence, we made assumptions that tended to favor the treatments.

Table 5.4. Key Model Assumptions

Assumptions	Rationale
Positive effects reported in the trial were assumed to continue in patients over the course of their lifetime.	This is an optimistic assumption that the treatment effect does not wane over time.
We assumed that treatment effects would lead to improved quality-of-life.	Despite the lack of trial evidence demonstrating an effect on general quality-of-life instruments the model assumes that improvements in acute and chronic events will result in improved quality-of-life.
Risk factors were multiplicative, i.e. risk factors were multiplied together to estimate a combined risk factor.	To estimate the likelihood of an event for those with multiple risk factors and to avoid the probability of an event being greater than 1.
Health-related quality of life is multiplicative.	To estimate the health-related quality of life of patients with multiple health states, it is recommended that a multiplicative assumption is used to reflect overlap in symptoms and to avoid implausibly low quality of life estimates.
All discontinuation occurs within the first year of treatment.	The trials report discontinuation at 48 or 52 weeks. It is assumed that patients that stay on treatment for 1 year will remain on treatment. This allows the model to estimate the potential benefit of life-time treatment. However it is possible that the magnitude of longer-term benefits seen with treatment in the model would not be realized due to discontinuation of treatment.
Opioid tolerance or dependence was only possible after patients had experienced 3 acute pain crises.	This assumption was instituted to recognize a potential consequence of the accumulation of acute pain crises.
The effects of baseline treatment (i.e., chronic transfusion, hydroxyurea, chelation therapy, etc.) were assumed to be captured in the usual care population.	Treatment rates in the source population used for usual care were similar to those for populations reported in the literature.
Drug-related treatment-emergent adverse events were treated with a physician visit, but were not modeled as having a significant effect on the health-related quality-of-life.	Treatment-related adverse events reported in the trials were expected to be transitory and treatable with over-the-counter medication or a visit to the physician.
Model results represent a mixed genotype population.	Model inputs are not available by genetic mutation. Treatment effects from the trials are representative of a mixed genotype population.
Caregivers experience health-related quality-of-life decrements proportionate to the patients. In this analysis it was assumed that caregivers decrements were 10% of the patients.	We considered this to be a large effect on the caregivers health-related quality-of-life which favors treatment of the patients.

Weight

The weight of the patients is of particular importance to the cost calculations for crizanlizumab. In the base case, we used the average weight reported in the SUSTAIN trial, 69.0 kg. At this weight, 4 vials of crizanlizumab are indicated per infusion and 15 grams of L-glutamine per day. The average weight in the SUSTAIN trial is lower than the average weight of the US population, 89.3 kg for 20-39 year-old males and 76 kg for 20-39 year-old females[97]. While one study using data from the average weight of a real-world study of patients at the Montefiore Medical Center in New York[98] found that patients with SCD are lighter than the general population, other studies have shown that: 1) adult patients with SCD are similar to the general population, with 4% underweight, 42% normal weight, 26% overweight and 28% obese[99]; and 2) children with SCD are similar in weight to the general population at birth and then "fell away before catching up at around 15 years of age in girls and 18 years in boys"[100,101].

In all cost calculations and in the base-case analysis we used the average weight of 69.0 kg, noting that this is an optimistic assumption for crizanlizumab. If patients with SCD are more similar in weight to the general population, the dose of L-glutamine would not change but patients receiving crizanlizumab would require 5 vials of crizanlizumab per infusion, which would increase the price by 25%. Ideally, manufacturers would report the distribution of patient weights in the trials or the distribution of number of vials used, as more patients may require 5 vials of crizanlizumab than 3 vials, and the impact on cost calculations can be significant.

Model Inputs

Clinical Inputs – Use of Real-World Data

A comprehensive literature review was undertaken to identify baseline rates of acute and chronic conditions of interest for the comparative cost-effectiveness model. Since the majority of patients with SCD receive health care coverage under Medicaid and/or Medicare, baseline rates were taken from CMS data when possible. A recently-published CMS report[102] summarized all patients with SCD over the age of 18 years with Medicare coverage as well as dual Medicaid and Medicare coverage.

Rates for baseline conditions of interest not available through CMS data reports, incidence rates of acute and chronic conditions in the model, and actual costs of both acute and chronic events were obtained through *de novo* evidence generation from a series of analyses using the Aetion Evidence Platform on a MarketScan claims dataset using the most recent data available, from Dec 31, 2002 to Dec 31, 2017. The Truven MarketScan databases capture longitudinal, individual-level administrative claims data from the US. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database, IBM MarketScan Research Databases for Life Sciences Researchers.[94] (See Appendix F for

full study protocol.) Data from the Truven MarketScan database covered approximately one-third of patients in the US with SCD and demonstrated a patient geographic distribution across the US in a similar pattern to the CMS data.

Baseline annual rates of acute and chronic events used in the model are presented in Tables 5.5 through 5.9 below. Inputs not available from the CMS report or MarketScan data were obtained from the literature.

Table 5.5. Baseline Annual Rates of Acute Chest Syndrome by Age

Age	Mean	Lower 95% CI	Upper 95% CI	Source[94]
0-1	0.075	0.07	0.09	MarketScan
2-4	0.101	0.09	0.12	MarketScan
5-12	0.107	0.10	0.11	MarketScan
13-17	0.092	0.09	0.11	MarketScan
18+	0.051	0.049	0.053	MarketScan

Table 5.6. Baseline Annual Rates of Stroke by Age*

Age	Mean	Lower 95% CI	Upper 95% CI	Source[94]
0-1	0.005	0.00	0.01	MarketScan
2-5	0.007	0.00	0.01	MarketScan
6-9	0.010	0.008	0.012	MarketScan
10-19	0.011	0.01	0.02	MarketScan
20+	0.021	0.020	0.023	MarketScan

*It was assumed that 35% of strokes would be major strokes resulting in more severe outcomes and higher costs[103].

Table 5.7. Baseline Annual Rates of Myocardial Infarction by Age

Age	Mean	Lower 95% CI	Upper 95% CI	Source[94]
0-12	0.000	0.000	0.000	MarketScan
13-17	0.0009	0.0004	0.0017	MarketScan
18+	0.0069	0.0062	0.0077	MarketScan

Table 5.8. Baseline Annual Rates of AKI/Renal Infarction by Age

Age	Mean	Lower 95% CI	Upper 95% CI	Source[94]
0-17	0.000	0.000	0.000	MarketScan
18+	0.0006	0.0004	0.0009	MarketScan

Table 5.9. Baseline Annual Chronic Complication Risks

Complication	Mean	Source	Justification
Opioid Tolerance/Dependence*	0.016	Elander et al. 2003[104]	Reported pain-related opioid tolerance for SCD patients, with good inter-rater reliability.
Neurocognitive Impairment	0.04	Schatz et al. 2001[105]	Reported deficit on any domain of neuropsychological evaluation with and without infarcts.
Fatigue	0.033	Sick Cell Survey	Survey of large US sample (N= 454).
Pulmonary Hypertension			
Age 0-1	0.0176	CMS 2016[40]	Administrative data analysis of 11,790 US Medicare beneficiaries. Reported higher risks than MarketScan data, selected to be optimistic towards treatments by allowing for a larger potential treatment effect.
Age 2-4	0.0176		
Age 5-12	0.0176		
Age 13-17	0.0176		
Age 18-30	0.0176		
Age 31-45	0.0609		
Age 46-54	0.1598		
Age 55-64	0.2018		
Age 65+	0.2289		
Heart Failure			
Age 0-1	0.0033	MarketScan[94]	Current, administrative data analysis of more than 33,174 sickle cell patients in the US. Risks used in the model provided life-time estimates similar to results from the CMS analysis. Data for adult patients was not stratified by age groups.
Age 2-4	0.0035	MarketScan[94]	
Age 5-12	0.0022	MarketScan[94]	
Age 13-17	0.0075	MarketScan[94]	
Age 18-30	0.0075	MarketScan[94]	
Age 31-45	0.0320	CMS 2016[40]	Administrative data analysis of 11,790 US Medicare beneficiaries. Data for adult patients was stratified by age groups.
Age 46-54	0.0772		
Age 55-64	0.0785		
Age 65+	0.0632		
Nephropathy, CKD			
Age 0-1	0.0038	MarketScan[94]	Current, administrative data analysis of more than 33,174 sickle cell patients in the US. Risks used in the model provided lifetime estimates similar to results from the CMS analysis. Data for adult patients was not stratified by age groups.
Age 2-4	0.0035	MarketScan[94]	
Age 5-12	0.0077	MarketScan[94]	
Age 13-17	0.0143	MarketScan[94]	
Age 18-30	0.0143	MarketScan[94]	
Age 31-45	0.0381	CMS 2016[40]	

Age 46-54	0.0945		Administrative data analysis of 11,790 US Medicare beneficiaries. Data for adult patients was stratified by age groups.
Age 55-64	0.1015		
Age 65+	0.0974		

*Opioid tolerance/dependence was estimated for patients that had experienced 3 or more acute pain crises in a year.
CKD: chronic kidney disease

Risk Factors and Correlations Between Conditions

An attempt was made to capture the risks of the different acute and chronic conditions. This was considered particularly important due to the multifaceted nature of the disease. Where available in the published literature, risk factors correlating each of the conditions were included in the model, as shown in Table 5.10. Much of the data demonstrated associations between conditions, rather than causation. In the base-case model, we made the assumption that these correlations would be causative in order to model the potential benefit of these treatments beyond the outcomes reported in the trials. This is an optimistic assumption, in that the model allows the outcomes reported in the trial to have an effect on other conditions not reported in the trials.

Table 5.10. Risk Factors for Acute and Chronic Conditions

Determinant	Consequence	Relative Effect	Source	Justification
Pulmonary hypertension	ACS	1.74	Agarwal et al. 2018[106]	Reported the odds and confidence interval of ACS for patients with SCD and pulmonary hypertension versus patients with SCD without pulmonary hypertension from a large number of hospitals in the US
Pulmonary hypertension	AKI/Renal infarction	1.70	Yeruva et al. 2016[107]	An analysis of 3,624 patients with SCD in the US that reported odds of new acute renal failure with hypertension
Nephropathy/ CKD	AKI/Renal infarction	2.00	Yeruva et al. 2016[107]	An analysis of 3,624 patients with SCD in the US that reported odds of new acute renal failure with CKD
Heart failure	AKI/Renal infarction	1.70	Yeruva et al. 2016[107]	An analysis of 3,624 patients with SCD in the US that reported odds of new acute renal failure with chronic heart disease
Nephropathy/ CKD	Myocardial infarction	2.26	Kokubo et al. 2009[108]	A large study (64,396 person years) of the effect of glomerular filtration rate on myocardial infarction
Pulmonary hypertension	Stroke	2.52	Agarwal et al. 2018[106]	Reported odds and confidence interval of acute stroke for patients with SCD and pulmonary hypertension versus patients with SCD without pulmonary hypertension from a large number of hospitals in the US
Nephropathy/ CKD	Stroke	1.25	Lee et al. 2010[109]	Meta-analysis of glomerular filtration rate on risk of stroke
AKI/Renal infarction	Nephropathy/ CKD	3.00	Yeruva et al. 2016[107]	An analysis of 3,538 patients with SCD in the US that reported odds of new CKD with acute renal failure
Myocardial infarction	Heart Failure	2.67	Tofovic et al. 2017[110]	An analysis of 15,500 patients with SCD in the US that reported odds of heart failure with myocardial infarction

ACS: acute chest syndrome, AKI: acute kidney injury, CKD: chronic kidney disease

For example, pulmonary hypertension and CKD are correlated with, and are considered in the model as risk factors for, stroke. In the model, those with pulmonary hypertension were 2.52 times more likely to experience stroke and those with CKD were 1.25 times more likely to experience a stroke. To estimate the likelihood of an event for those with multiple risk factors, we assumed that the risk was multiplicative, i.e., risk factors were multiplied together to estimate a combined risk factor.

The above risk factors were applied to the baseline rates previously reported. The use of these risk factors resulted in a population similar to that reported by CMS in 2016[102] (see the validation section below).

Mortality Probabilities

Annual mortality probabilities were estimated from Hassell et al. 2010 (Appendix Table E2). The model allows for increases in mortality due to acute pain crises, ACS, myocardial infarction, AKI/renal infarction, pulmonary hypertension, heart failure, CKD, and stroke. To risk adjust the mortality probabilities for each additional risk factor in the model, the age-specific estimates from the literature were divided by the risk of death from each of the chronic conditions.

$$\frac{Death\ Age}{(\ pHTN_{RF} \times HF_{RF} \times CKD_{RF})}$$

pHTN: pulmonary hypertension, HF: heart failure, CKD: chronic kidney disease, RF: risk factor for death

The annual relative effect of acute pain crises on death was found to range from 1.2 to 2.68[111-113] and of ACS on death from 1.03 to 1.5 (Table 5.11).[113,114] A relative effect of 1.2 was used for acute pain crises, as the study best represented the annual risk of death per event.[114] Using the baseline annual risk of death estimated from Hassell et al. 2010, the annual risk was converted to a 2-week risk to reflect the cycle length of the model. This conversion means that deaths that would really happen over the course of the year occur in the model during the two-week cycle in which the acute pain crisis occurs; this has the effect of decreasing life-expectancy after an acute pain crisis. The same conversion was used for ACS, using the average of the two published risk factors. There is also an increased probability of death included in the model for those who experience a stroke. In the first two weeks after a stroke there is a 0.074 probability of death. No published risk factors were found for heart failure or myocardial infarction in patients with SCD, so it was assumed that these risk factors were the same as for pulmonary hypertension. The results of combining these data are reported in the validation section below.

Table 5.11. Risk Factors for Death

Complication	Relative Effect	Source	Justification
Acute pain crisis	1.2	Darbari et al. 2013[112]	Reported the annual risk of death per pain crisis.
ACS	1.27	Average of Platt et al. 1994 and Maitra et al. 2017[113,114]	Report the risk of death with ACS versus no ACS adjusted for demographics.
Myocardial infarction	12.57	Assumption (same as for pulmonary hypertension)	This was an optimistic assumption since the higher relative effects on death decrease the incremental cost-effectiveness ratios.
AKI/Renal infarction	9.57	Lanzkron et al. 2013[115]	Renal disease was found to be associated with death in 16,654 sickle cell-related deaths.
Pulmonary hypertension	12.57	Gladwin et al. 2012[116]	Report that for patients with SCD, TRV≥2.5m/s was associated with a 9.24 to 15.9 risk ratio for early death, with an average of 12.57.
Heart failure	12.57	Assumption (same as for pulmonary hypertension)	This was an optimistic assumption since the higher relative effects on death decrease the incremental cost-effectiveness ratios.
Nephropathy, CKD	9.57	Lanzkron et al. 2013[115]	Renal disease was found to be associated with death in 16,654 sickle cell-related deaths.

ACS: acute chest syndrome, AKI: acute kidney injury, CKD: chronic kidney disease

Risk factors for death are applied during each cycle that a patient is considered to have the health state. Once a chronic condition occurs, the patients will have it for life, so the risk factor is applied in every cycle for the rest of their life. For acute conditions, they are applied for the cycle in which the acute condition occurs, but then patients go back to having the baseline probability of death. This means that when a patient with heart failure has a myocardial infarction, they have the risk factor for both myocardial infarction and heart failure for that cycle and then go back to having only the heart failure risk.

Treatment Effect

We used treatment effects from the clinical trials (Table 5.12). Each trial reported the relative effect of treatment on acute pain crises. Although the trial results for voxelotor were not statistically significant, the reported magnitude of effect for voxelotor was used in its base case as well. The relative effect on acute pain crisis was used directly in the model. Despite the lack of information of treatment effect on other outcomes of interest, we assumed that acute events and

chronic conditions could also be impacted by reducing the number of acute pain crises. Voxelotor was the only treatment to report a statistically significant difference in hemoglobin. The model was programmed to also allow for the effect of changes in hemoglobin on risk for acute and chronic conditions. The relative effect of hemoglobin level on stroke, fatigue, CKD, and pulmonary hypertension were obtained from the literature and included in the model.

Table 5.12. Treatment Effects

Treatments	Relative Effect on Acute Pain Crises	Change in Hemoglobin (g/dL)	Source
Crizanlizumab	0.547	0	SUSTAIN trial[36]
Voxelotor	0.868	1.2	HOPE trial[37]
L-glutamine	0.730	0	FDA Analysis[38]

g/dL: grams per deciliter

The effects of acute pain crises on acute events and chronic conditions were found in the literature, and are shown in Table 5.13. For example, patients who experience an acute pain crisis are 58.67 times more likely to have an ACS in the next cycle and patients who experience an acute pain crisis are 4.12 time more likely to develop pulmonary hypertension in the next cycle.

Table 5.13. Acute Pain Crisis as a Risk Factor for Acute and Chronic Conditions Used in the Model

Treatments	Risk Factor Used in Model	Source	Justification
Acute Events			
ACS	58.67	Shah et al. 2019[111]	An analysis of 20,909 US patients with SCD enrolled in Medicaid reported that patients with VOC were more likely to have an ACS.
Myocardial infarction	3.00	Bode-Thomas 2011[117]	An analysis of children with SCD reported that patients with SCD and VOC were 3 times more likely to have myocardial infarction than patients with SCD but not VOC.
AKI/Renal infarction	3.00	Assumption	No studies were found on the effect of VOC on AKI/renal infarction. It was assumed that the relative effect on AKI would be most similar to myocardial infarction.
Stroke	2.26	Shah et al. 2019[111]	An analysis of 20,909 US patients with SCD enrolled in Medicaid reported that patients with VOC were more likely to have a stroke.
Chronic Conditions			
Pulmonary hypertension	4.12	Shah et al. 2019[111]	An analysis of 20,909 US patients with SCD enrolled in Medicaid reported that patients with VOC were more likely to develop pulmonary hypertension.
Heart Failure	1.185	Van Tuijn et al. 2010[13]	An analysis of 104 adult patients with SCD reported that patients with more than 2 VOCs over a 5 year period were more likely to develop any form of organ complication. No studies were found on the effect of VOC on heart failure.
Nephropathy, CKD	1.185	Van Tuijn et al. 2010[13]	An analysis of 104 adult patients with SCD; reported that patients with more than 2 VOCs over a 5-year period were more likely to develop any form of organ complication. No studies were found on the effect of VOC on CKD.

ACS: acute chest syndrome, AKI: acute kidney injury, CKD: chronic kidney disease

The relative effect of hemoglobin level on stroke and fatigue were obtained from the literature and included in the base case of the model. The reported difference of 1.2 g/dL for voxelotor was used in the model. It was assumed there would be a constant treatment effect as long as patients

continued to use voxelotor, i.e., that patients maintained a 1.2 g/dL effect as long as they continued treatment. To estimate the effect of 1.2 g/dL change in hemoglobin, the effect size was assumed to be exponential:

$$RE^H = 0.602^{1.2} = 0.544$$

where RE is the relative effect reported in the literature and H is the hemoglobin difference reported in the trial (Table 5.14).

There was mixed evidence on the relationship between hemoglobin level and both CKD and pulmonary hypertension. One study suggested that lower hemoglobin was associated with hyperfiltration; however no data were reported.[118] Another study showed no difference in hemoglobin levels between patients with normoalbuminuria and those with micro- or macroalbuminuria.[119] Mixed results were reported on the association of hemoglobin and estimated glomerular filtration rate (eGFR) which measures kidney function.[120] Derebail et al. used a multiregression analysis and reported that a 1 g/dL increase in hemoglobin was associated with 0.64 odds of CKD in hemoglobin SC disease and sickle-β+-thalassemia but no effect in homozygous SCD or sickle-β0-thalassemia.[121] To capture the possibility of an effect on CKD, we assumed that a 1 g/dL increase in hemoglobin would decrease the risk of CKD by a factor of 0.64. Adjusted for a 1.2 g/dL increase, this resulted in a risk factor of 0.56.

We also explored the effect of hemoglobin changes on pulmonary hypertension. Generally, studies evaluated the difference between those with less than 2.5 m/s tricuspid regurgitant jet velocity and those with 2.5 or more. Four studies showed no statistically significant differences in average hemoglobin between groups.[122-125] One study found that for every 1.0 g/dL increase in hemoglobin, TRV decreased by 13%.[126] To capture the possibility of an effect on pulmonary hypertension, we used the results of a meta-regression which reported a 1% (95%CI, -8% to 6%) higher prevalence of tricuspid regurgitant velocity of 2.5 m/s or greater. This 1% difference was reported for a population with an average age of 22 years, so an annual difference was estimated by assuming the difference would accumulate over the 22 years and then be constant for a patient's life.

No other outcomes in the model were assumed to be directly affected by changes in hemoglobin. However, other acute events and chronic conditions could be affected indirectly in the model as, for example, a reduction in nephropathy/CKD was included in the model as a risk factor for AKI/renal infarction, myocardial infarction, and stroke. Therefore, a treatment that reduces nephropathy/CKD is assumed to also indirectly reduce these acute events.

Table 5.14. Effects of a 1 g/dL Change in Hemoglobin

Condition	Relative Effect	Effect for Voxelotor Used in Model	Source	Justification
Stroke	0.602	0.544	Ohene-Frempong et al. 1998[127]	A longitudinal study of 4,082 US patients with SCD over 10 years reports the relative risk of stroke of 1.61 per 1 g/dL decrease in hemoglobin.
Fatigue	0.71	0.67	Prochaska et al. 2017	An analysis of 666 hospitalized patients with anemia in the US reported probability of fatigue for patients with hemoglobin between 8-9 g/dL and patients with >9 g/dL; selected population with the largest difference to provide most optimistic estimate of effect.
Nephropathy, CKD	0.63	0.56	Derebail et al. 2019[121]	Observational study of 427 patients with SCD reporting higher hemoglobin level associated with lower probability of CKD.
	Reduction in Annual Probability	Effect for Voxelotor Used in Model	Source	Justification
Pulmonary hypertension	0.0005	0.0006	Caughey et al. 2015[122]	An analysis of 135 US patients with SCD reports 1% change in prevalence of elevated pulmonary artery systolic pressure between hemoglobin of 8.4 g/dL and 9.3 g/dL.

CKD: chronic kidney disease

AEs

We included serious drug-related treatment-emergent adverse events in the model as reported in the respective clinical trials (Table 5.15). Each AE was assumed to require a physician visit at a cost of $175 per visit, based on the cost of a level 5 physician visit. We did not model any quality of life impacts due to AEs, as these were generally transitory.

Table 5.15. Treatment-Related Adverse Events

Treatment	Drug-Related Treatment-Emergent Adverse Events	Comment	Source
Crizanlizumab	0.15	Annual rate of serious AEs during the trial	Kutlar et al. 2019[89]
Placebo arm of SUSTAIN trial	0.05		
Voxelotor	0.034	Proportion of patients that experienced a serious AE during the trial	Vichisky et al. 2019[37]
Placebo arm of HOPE trial	0.011		
L-glutamine	0.021	Proportion of patients that experienced a severe AE during the trial	L-Glutamine Sponsor Briefing Document[128]
Placebo arm of trial	0.018		

AE: adverse event

Utilities

A systematic literature review was undertaken to investigate data on the health-related quality of life for patients with SCD. Much of the literature was collected on patients from the United Kingdom (UK). Where possible values from the US were prioritized for use in the model; however, US and UK values were generally similar.

Utilities were applied to the proportion of the cohort in each health state in the model. For example, an otherwise healthy patient who experienced ACS would have a utility of 0.581 for the 2-week cycle that they experienced ACS. In the base case for patients experiencing multiple conditions, it was assumed that utilities were multiplicative. For example, a patient with opioid tolerance or dependence would have a utility of 0.64, but during an ACS the utility would be 0.64 X 0.581 = 0.37. The multiplicative approach was chosen since it was optimistic for the treatments. Alternatively, an additive assumption can be made; using the reported disutilities, this would result in the same patient having a utility of 0.64 – 0.129 = 0.51. The additive assumption was tested in a sensitivity analysis.

Anie et al. 2012 reported utilities for acute pain crisis at admission to hospital, discharge and 1 week after discharge. Anie et al. 2002 found that "the organization and cost of health care in the UK differs from that in the USA, as do the links between primary care and hospital services" but that "the pain experience of adults with sickle cell disease in the UK resembles that of cohorts assessed

in the USA ", suggesting that the decrement in health-related quality-of-life may be similar for the pain experience itself, even if the subsequent health care is different[129]. We assumed that patients experiencing an acute pain crisis would have the admission utility for 1 week and the discharge utility for 1 week. This is an optimistic assumption for treatments for pain crisis as it assumes a decrement to the health-related quality-of-life from a pain crisis for 2 weeks in total. In the survey data provided by Sick Cells, only 46% of respondents reported that their most recent pain crisis lasted more than 4 days.

Table 5.16. Utility Estimates for Health States

Health State	Model Utility	Model Disutility	Source Value	Source	Justification
Uncomplicated SCD	0.80		0.80	Anie et al. 2012 [130]	Based on an algorithm from a UK population with a relatively high utility, that is optimistic for the treatments.
Acute pain crisis (admission)	0.44	0.36	0.39	Anie et al. 2012 [130]	Longitudinal study of 510 adult patients with SCD admitted to hospital; only utilities collected on pain crises.
Acute pain crisis (discharge)	0.70	0.1	0.65		
Acute pain crisis (1 week follow-up)			0.75		
Two-week crisis assuming 7 days of severe pain (admission) and 7 days of less severe pain (discharge)*	0.57	0.23		Calculated	Optimistic assumption given that 54% of survey respondents reported 4 days or fewer of pain.
ACS	0.56	0.13	0.56	NICE CG 143[131]	No SCD-specific data identified; used in NICE analysis.
Myocardial infarction	0.67	0.13	0.13	Clarke et al. 2002 [132]	No SCD-specific data identified; used regression model to determine additional effect of myocardial infarction on utility.
AKI/Renal infarction	0.67	0.14	0.14	Villeneuve et al. 2016 [133]	No SCD-specific data identified; systematic literature review.
Stroke (major)	0.24	0.57	0.57	NICE CG 143[131]	No SCD-specific data identified; assumed utility of experiencing any stroke is equal to long-term decrement of major stroke
Stroke (minor)	0.64	0.16	0.16		
Post-stroke based on the proportion of major stroke (0.35)	0.50	0.30		Calculated	No SCD-specific data identified; used in NICE analysis.
Opioid tolerance/dependence	0.73	0.07	0.07	Krebs et al. 2018 [134]	No SCD-specific data identified.
Pulmonary hypertension	0.68	0.12		Assumption	Similar to heart failure and CKD.
Heart failure	0.68	0.12	0.12	Clarke et al. 2002 [132]	No SCD-specific data identified; used regression model to determine additional effect of heart failure.

Nephropathy, CKD	0.67	0.14	0.14	Villeneuve et al. 2016 [133]	No SCD-specific data identified; assumed to be similar to acute kidney injury.
Neurocognitive impairment	0.77	0.05	0.05	Stites et al. 2018 [135]	No SCD-specific data identified; used regression model to determine additional effect of cognitive difficulties.
Fatigue	0.68	0.12	0.12	Naess et al. 2012 [136]	No SCD-specific data identified; used regression model to determine the additional effect of fatigue in patients with ischemic stroke.

ACS: acute chest syndrome, AKI: acute kidney injury, CKD: chronic kidney disease, SCD: sickle cell disease
*The model allows for the length of severe pain to be adjusted. Currently, it is assumed to be 7 days.

Economic Inputs

Drug Acquisition Costs

We obtained the list prices for crizanlizumab and L-glutamine.[137] The reported list price of voxelotor (Oxbryta) is $10,417 per month.[138]

We applied estimated branded drug discount rates to obtain net pricing estimates. Because crizanlizumab and voxelotor were recently approved, there are no data on net price available yet. Because net prices are not yet known, we used the average branded drug discount in the US of 27% as an estimate of these drug's net prices.[139] Net price data for L-glutamine were not available in the SSR net price database,[140] so we used the FSS price as the net price for this drug.[141] As part of usual care, we used the average of generic prices for hydroxyurea. The proportion of patients using hydroxyurea in the usual care arm of the model was assumed to be 64%. This was similar to the proportions reported in the voxelotor and crizanlizumab trials where the proportion of patients found to be using hydroxyurea were 64% and 63%, respectively. As noted previously, this is different from previous studies that have reported 15% use of hydroxyurea.[94]

Table 5.17. Drug Costs

Drug	WAC per Package/Vial	Discount From WAC	Net Price Per Package/Vial	Net Price per Year§
Crizanlizumab (Adakveo®)	$2,357/vial	27%	$1,721	$96,354
Voxelotor (Oxbryta®)	$10,417	27%	$7,604	$92,584
L-glutamine (Endari®)*	$1,110/package	26%	$822.61†	$30,046
Hydroxyurea‡	$88.05/100 capsules	--	--	$322 - $2,251

NA: not available, WAC: wholesale acquisition cost
*Price per package of 60 5g packets
†Federal Supply Schedule (FSS) price as of March 1, 2020
‡Average of generic prices for 100 500mg oral capsules
§1 year = 365.25 days or 52 weeks

Non-Drug Costs

As described above, actual costs of both acute (Table 5.18) and chronic (Table 5.19) events were obtained through *de novo* evidence generation from a series of analyses using the Aetion Evidence Platform on a Marketscan claims dataset using the most recent data available, from Dec 31, 2002 to Dec 31, 2017. The Truven MarketScan databases capture longitudinal, individual-level administrative claims data from the United States. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database. (See Appendix F for full study protocol).

Table 5.18. Cost per SCD Complication

Incremental Cost in the Year of Event/Diagnosis (per Event)	Estimate	SD	Source
Acute Pain Crisis			
Age < 18	$12,980	$33,604	MarketScan[94]
Age ≥ 18	$13,735	$24,576	MarketScan[94]
ACS			
Age < 18	$22,701	$24,332	MarketScan[94]
Age ≥ 18	$29,896	$49,104	MarketScan[94]
Myocardial infarction	$53,458	$81,781	MarketScan[94]
AKI/Renal infarction	$8,205	NR	Yeruva et al. 2016[107]
Stroke			
Age < 18	$129,956	$243,770	MarketScan[94]
Age ≥ 18	$57,780	$94,745	MarketScan[94]

ACS: acute chest syndrome, AKI: acute kidney injury, NR: not reported

Table 5.19. Annual Cost of Chronic Complications

	Estimate	(95% CI)	Source
Pulmonary hypertension	$19,343	(10,697, 27,989)	MarketScan[94]
Heart failure	$32,505	(21,405, 43,605)	MarketScan[94]
Nephropathy, CKD	$20,708	(13,947, 27,468)	MarketScan[94]
Neurocognitive impairment	$11,687	(1,430, 21,944)	MarketScan[94]
Fatigue	$4,398	(588, 8,208)	MarketScan[94]
Post-stroke	$9,807	NR	MarketScan[94]
Opioid tolerance/dependence	$17,345	(-1,151, 35,841)	MarketScan[94]

CI: confidence interval, CKD: chronic kidney disease, NR: not reported

According to the MarketScan data, 11% to 29% of patients are on chronic transfusion and up to 5 in 10,000 experience iron overload, depending on their age. Age-specific proportions were used to calculate chronic transfusion costs using the annual cost of chronic transfusion from Blinder et al. 2013 and iron overload costs using costs calculated from the MarketScan data (Table 5.20).

Table 5.20. Other Health Care Cost Parameters

	Estimate	Lower (-20%)	Upper (+20%)	Source
Physician Visit	$175	$140	$210	Level 5 Physician Visit
Transfusion Cost (per year)	$36,305	$29,044	$43,566	Blinder et al. 2013 [142]
Iron Overload (per event)	$9,137	$7,309	$10,964	MarketScan Data[94]

Societal Perspective Inputs

A modified societal perspective is included as a dual base case, using out-of-pocket costs, productivity losses, caregiver HRQoL, and school attendance.

Huo et al. 2018 report that out-of-pocket costs for sickle cell patients are $1,293 per year. This was calculated to be approximately 2% of the usual care arm's annual health state costs in the model. To estimate an effect of treatment on out-of-pocket costs it was assumed that 2% of the health state costs each cycle would be out-of-pocket, so treatments that reduce health state costs by reducing acute and chronic conditions would have lower out-of-pocket costs.

The survey data provided by Sick Cells reports that patients with SCD miss 24% of work due to their disease, experience decreased productivity at work 45% of the time and that the overall productivity lost is 65%. This is similar to the Rizio et al. 2020 study that reported that patients with 4 or more pain crises per year had an overall productivity loss of 63%[60]. The average annual salary in the US in 2018 was $51,960.[143] Using the productivity lost from the Sick Cells survey, a patient with SCD has an expected lost productivity of $33,816 per year (65% X $51,960). Rizio et al. 2020[60] report that patients with more frequent pain crises in the past 12 months and patients with more severe pain crises have greater absenteeism and greater overall productivity loss. In particular they report that patients with fewer than 4 pain crises per year have an overall work productivity loss of 49.3%. In the model, it was assumed that patients in the usual care arm of the model would have lost productivity similar to that reported in the Sick Cells survey of $33,816 per year, while patients in the treatment arm would have a reduced productivity loss of $26,863 per year using the overall productivity lost in Rizio et al[60]. Note that assuming this large a difference in productivity lost, i.e. 65% in the usual care arm and 49.3% in the treatment arm, is an optimistic assumption as both arms have fewer than 4 pain crises per year.

School attendance and caregiver burden were estimated based on the number of acute events experienced by patients. For school attendance, it was assumed that for each acute event (i.e. pain,

ACS, myocardial or renal infarction or stroke) a patient between the ages of 5-18 would miss 7 days of school. For caregiver burden, it was assumed that for each acute pain event the caregiver would miss 7 days of work. Using 7 days of missed school and work for caregivers is an optimistic assumption in favor of the new treatments, as respondents in the Sick Cells survey stated that during their most recent pain crisis they were unable to go to work on average for 4.8 days or to go to school for 4.2 days. Finally, work days were valued using the average US salary of $51,960 per year.[143]

An attempt was also made to estimate the decrement in the quality-of-life of caregivers. It was assumed that the caregiver would experience 10% of the disutility experienced by the patient (see Table 5.16). For example, for every ACS experienced by the patient the caregiver would also have a 0.0129 decrease in their utility. It was also assumed that the death of a patient would result in a 0.05 decrease in utility for the caregiver until the end of the model.

Model Analysis

The model estimated the average survival, quality-adjusted survival, drug cost, complication cost, and number of acute complications per patient. Time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Long-term estimates of costs, quality-adjusted life year (QALYs), equal-value life years gained (evLYG), and life-years (LY) were discounted at 3% per year following ICER guidelines, to account for the opportunity cost of current spending and preference for current over future benefits.   A more detailed description of evLYG calculations can be found in Appendix E. We calculated the incremental results for each intervention versus usual care alone as the incremental cost per LY, evLYG, and QALY, as well as the incremental cost per pain crisis avoided and per 1 g/dL increase in hemoglobin.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over the minimum numbers of simulations necessary to achieve statistical convergence, then calculating 95% credible range estimates for each model outcome based on the results.

Scenario Analyses

Two scenario analyses have been provided to demonstrate the cost-effectiveness of treatments in different populations. The first population had a higher pain crisis rate, with a baseline of 10 acute pain crises per year. The second population reflects a younger cohort, using the starting age of 5 years, the minimum age for which L-glutamine is indicated, and 16 years, the minimum age for which crizanlizumab is indicated. We also performed threshold analyses to determine drug prices

that would achieve a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Model Validation

We used several approaches to validate the model. First, we shared preliminary methods, inputs, and model assumptions with manufacturers, patient groups, and clinical experts. Based on feedback from these different groups on our methodology and calculations, we refined our approach and data inputs used in the model, as relevant. Second, we varied model input parameters to evaluate face validity of changes in results. Third, we performed model verification for model calculations using internal reviewers. Finally, following publication of the draft report, we made the model available to the manufacturers and patient groups for a review period of three weeks. Feedback from review of the model and draft report were considered when revising the draft report.

A number of important changes were made to the model since the first draft including,

1. a societal analysis incorporating patient productivity lost, caregiver burden and utility and out-of-pocket costs
2. treatment effect of L-glutamine reduced from 0.91 to 0.73
3. utility of uncomplicated SCD increased from 0.71 to 0.801
4. calculating the price of voxelotor based on 30 pills per package from 28 pills per package
5. calculating the price of crizanlizumab using 4 vials per infusion, based on lower weight of SCD patients
6. addition of infusion costs for crizanlizumab
7. updated price of L-glutamine of $822.61

5.3 Results

Base-Case Results from Health Care and Societal Perspectives

Health Care Perspective

All base-case results shown here are discounted at 3% for both costs and outcomes. (Undiscounted results for each drug are shown in Appendix Tables E3-E5.) The base-case results show the life-time costs for a patient on usual care from age 24 are approximately $1.2 million. The model estimates that usual care patients with a baseline risk of 3 acute pain crises per year are expected to experience 43 acute pain crises over their lifetime. Not all patients will have a myocardial or AKI/renal infarction or stroke; the model estimates a rate of 18 per 100 myocardial infarctions, 2 per 100 AKI/renal infarctions, and 59 per 100 with stroke. Each treatment below is compared to the same usual care arm.

Treatment costs for crizanlizumab are approximately $970,000 over the lifetime, with cost-savings of approximately $98,000 from avoided acute and chronic conditions (Table 5.21). Cost offsets are due to avoiding costs of acute and chronic conditions, which are lower for patients on crizanlizumab than with usual care alone. However, these cost offsets are attenuated by the additional costs of longer life with costly chronic conditions. The model estimates that crizanlizumab patients will experience 27 acute pain crises over their lifetime and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction and stroke (Table 5.21). Incremental cost-effectiveness of crizanlizumab compared to usual care is estimated to be $432,000 per life year (LY) gained, $509,000 per evLYG and $1.1 million per QALY gained.

Table 5.21. Results for the Base Case for Crizanlizumab versus Usual Care Alone: Health Care Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental Cost-Effectiveness	
Treatment Cost	-	$970,000	$970,000	-	
Other Cost	$1,174,000	$1,075,000	-$98,000	-	
Total Cost	$1,174,000	$2,046,000	$872,000	-	
Acute Pain Crises	43.02	26.85	-16.18	$54,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life-years	14.34	16.36	2.02	$432,000	per LY gained
evLYG	8.07	9.78	1.71	$509,000	per evLYG
QALYs	8.07	8.87	0.80	$1,086,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Treatment costs for voxelotor are approximately $1.1 million over the lifetime (Table 5.22). The model estimates that voxelotor patients will experience 42 acute pain crises over their lifetime (Table 5.22), and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction and stroke. Patients on voxelotor also experience an average increase in hemoglobin levels of 1.2 g/dL. Given the assumption that rises in hemoglobin with voxelotor produce benefits analogous to higher hemoglobin levels in other settings, this results in patients on voxelotor having the fewest stroke events over their lifetime, 37 per 100 patients. Incremental cost-effectiveness of voxelotor compared to usual care is estimated at approximately $550,000 per LY gained, $589,000 per evLYG, and $1.1 million per QALY gained. Note that these results rely on the inclusion of several assumptions that tended to favor the treatment. Despite the lack of information of treatment effect on other outcomes of interest, we assumed that acute events and chronic conditions would be impacted by the (non statistically significant) reduction in number of acute pain crises, and that there was an effect of changes in hemoglobin on risk for acute and chronic conditions including stroke, fatigue, chronic kidney disease, and pulmonary hypertension.

Table 5.22. Results for the Base Case for Voxelotor versus Usual Care Alone: Health Care Perspective

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio	
Treatment Cost	-	$1,114,000	$1,114,000	-	
Other Cost	$1,174,000	$1,177,000	$3,000	-	
Total Cost	$1,174,000	$2,291,000	$1,117,000	-	
Acute Pain Crises	43.02	41.52	-1.50	$743,000	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$57,000	per g/dL per year*
LYs	14.34	16.37	2.03	$550,000	per LY gained
evLYG	8.07	9.96	1.90	$589,000	per evLYG
QALYs	8.07	9.10	1.03	$1,082,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year
*It is assumed that patients on voxelotor maintain the 1.2 g/dL hemoglobin improvement throughout their life. This number is the total incremental cost divided by the improvement in hemoglobin divided by life-expectancy or the number of years it is assumed the improvement will be maintained. This represents the cost of improving an individual's hemoglobin by 1g/dL each year.

Treatment costs for L-glutamine are approximately $299,000 over the lifetime, with cost-savings of approximately $59,000 from avoided acute and chronic conditions (Table 5.23). The model estimates that L-glutamine patients will experience 34 acute pain crises over their lifetime and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction, and stroke (Table 5.23). Incremental cost-effectiveness of L-glutamine compared to usual care is estimated to be approximately $238,000 per LY gained, $270,000 per evLYG, and $604,000 per QALY gained.

Table 5.23. Results for the Base Case for L-glutamine versus Usual Care Alone: Health Care Perspective

Treatment	Usual Care	L-glutamine	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$299,000	$299,000	-	
Other Cost	$1,174,000	$1,115,000	-$59,000	-	
Total Cost	$1,174,000	$1,414,000	$240,000	-	
Acute Pain Crises	43.02	33.61	-9.41	$26,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	14.34	15.35	1.01	$238,000	per LY gained
evLYG	8.07	8.96	0.89	$270,000	per evLYG
QALYs	8.07	8.47	0.40	$604,000	per QALY gained

evLYG: equal value life year gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.24 reports the life-time discounted acute events. In all cases patients with usual care alone are more likely to experience an acute event. Patients on crizanlizumab experience the fewest acute pain crises, MI and renal infarction events. This is because of the large treatment effect of crizanlizumab on acute pain crises and the relative effect of acute pain crises on each of the other acute events in the model. Patients on voxelotor experience the fewest stroke events because of the relative effect of improvements in hemoglobin on strokes, with smaller impacts on other events.

Table 5.24. Comparison of Acute Events

Treatment	Usual Care	Crizanlizumab	Voxelotor	L-glutamine
Acute Pain Crisis	43.02	26.85	41.52	33.61
ACS	0.95	0.90	0.89	0.94
MI	0.18	0.17	0.18	0.18
RI	0.02	0.02	0.02	0.02
Stroke	0.59	0.56	0.37	0.57

ACS: acute chest syndrome, MI: myocardial infarction, RI: renal infarction

Table 5.25 reports the prevalence of chronic diseases accounted for in the model at different ages. These results suggest crizanlizumab improves pulmonary hypertension and CKD after age 24 and heart failure until after 50 years of age. Voxelotor and L-glutamine improve pulmonary hypertension, chronic kidney disease, and heart failure after 24 years of age. The model assumes no direct treatment effects on chronic conditions for crizanlizumab or L-glutamine. However, the model does assume that acute pain crises have an effect on each of the chronic conditions. Therefore, treatments that reduce acute pain crises reduce chronic conditions, and treatments that

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reduce acute pain crises more have a larger impact on chronic conditions. The model also accounts for improvements in hemoglobin, as discussed above. In some cases, prevalence in the treated population is higher than the prevalence in the usual care group. This is due to longer life expectancy in the treatment arms.

Table 5.25. Comparison of Chronic Disease Prevalence at Different Ages in the Model

	Model			
	Usual care	**Crizanlizumab**	**Voxelotor**	**L-glutamine**
Age	pHTN (%)			
24	34%	34%	34%	34%
38	63%	58%	56%	60%
50	82%	77%	75%	79%
59.5	91%	88%	88%	89%
70	98%	96%	96%	96%
	HF (%)			
24	13%	13%	13%	13%
38	35%	34%	30%	30%
50	51%	51%	43%	43%
59.5	57%	61%	48%	49%
70	55%	61%	44%	46%
	CKD (%)			
24	21%	21%	21%	21%
38	39%	35%	31%	38%
50	56%	51%	43%	54%
59.5	64%	62%	50%	64%
70	69%	66%	54%	69%

CKD: chronic kidney disease, HF: heart failure, pHTN: pulmonary hypertension

Modified Societal Perspective

The economic value of lifetime productivity gains from treatment compared to usual care alone ranged from approximately $155,000 for crizanlizumab and voxelotor to $129,000 for L-glutamine. Crizanlizumab had the highest out-of-pocket costs avoided, caregiver burden avoided, and improvement in school attendance, as these outcomes were closely related to acute events. Voxelotor had the most improvement in caregiver QALYs, as these were more directly related to the chronic health states. We calculated the incremental cost-effectiveness ratios from a societal perspective by subtracting the productivity gained, the out-of-pocket costs avoided, and the caregiver burden avoided from the total cost differences and adding the caregiver QALYs to the patient QALYs. The cost per QALY of L-glutamine was affected the most, as the productivity gained was substantial compared to the total cost of the treatment.

Table 5.26. Results for the Base Case for Crizanlizumab, Voxelotor, and L-glutamine versus Usual Care Alone: Modified Societal Perspective

Treatment	Crizanlizumab	Voxelotor	L-glutamine
Productivity Gained	$155,300	$155,600	$129,000
Out-of-Pocket Costs Avoided	$2,400	$40	$1,400
School Attendance*	112	40	66
Caregiver Burden Avoided	$16,200	$1,800	$9,400
Caregiver QALYs	0.05	0.08	0.03
Cost per LYG	$364,000	$474,000	$121,000
Cost per evLYG	$416,000	$488,000	$134,000
Cost per QALY	$859,000	$866,000	$289,000

*To capture an effect on school attendance the costs and outcomes were estimated for a population being treated from 5 years old.

Sensitivity Analysis Results

One-Way Sensitivity Analysis

Health Care Perspective

Sensitivity analysis demonstrates that, for all three treatments, the cost of the treatments, the utility of uncomplicated sickle cell disease, and the treatment effect on acute pain crises are the major drivers of cost per QALY (Figures 5.2-5.4). The effect of treatment on hemoglobin level and the impact of hemoglobin level on stroke and CKD also had relatively large impacts on the estimated cost per QALY of voxelotor. However, in no case did the estimated cost per QALY fall below $350,000 for any of the drugs.

Figure 5.2. Sensitivity Analysis of Crizanlizumab Compared to Usual Care: Health Care Perspective

Tornado diagram
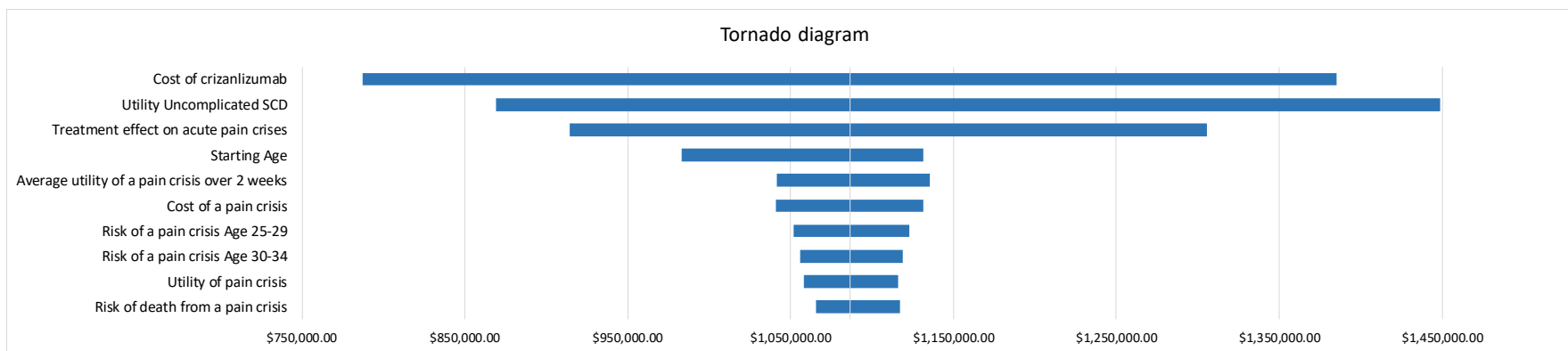
Figure 5.3. Sensitivity Analysis of Cost per QALY for Voxelotor Compared to Usual Care: Health Care Perspective

Tornado diagram
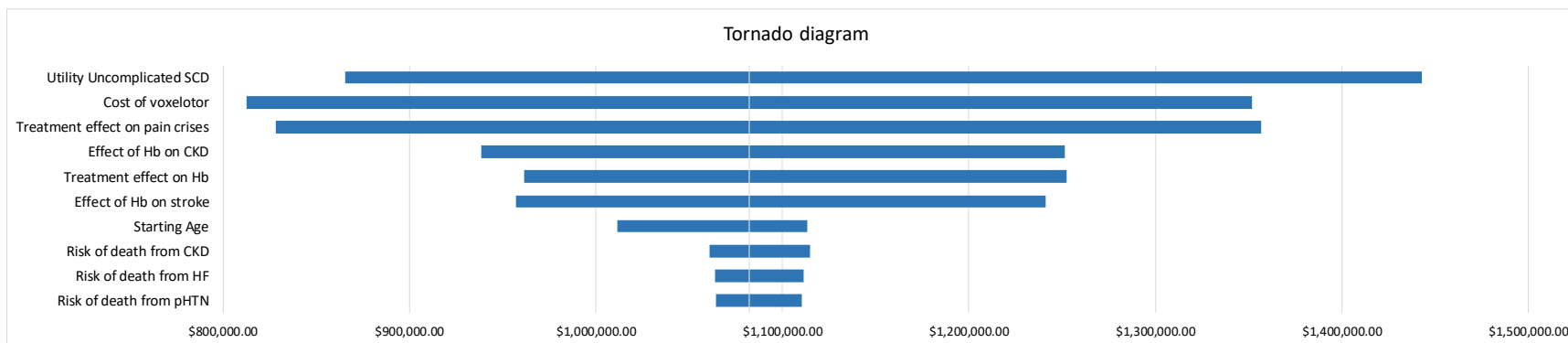
Figure 5.4. Sensitivity Analysis of Cost per QALY for L-Glutamine Compared to Usual Care: Health Care Perspective
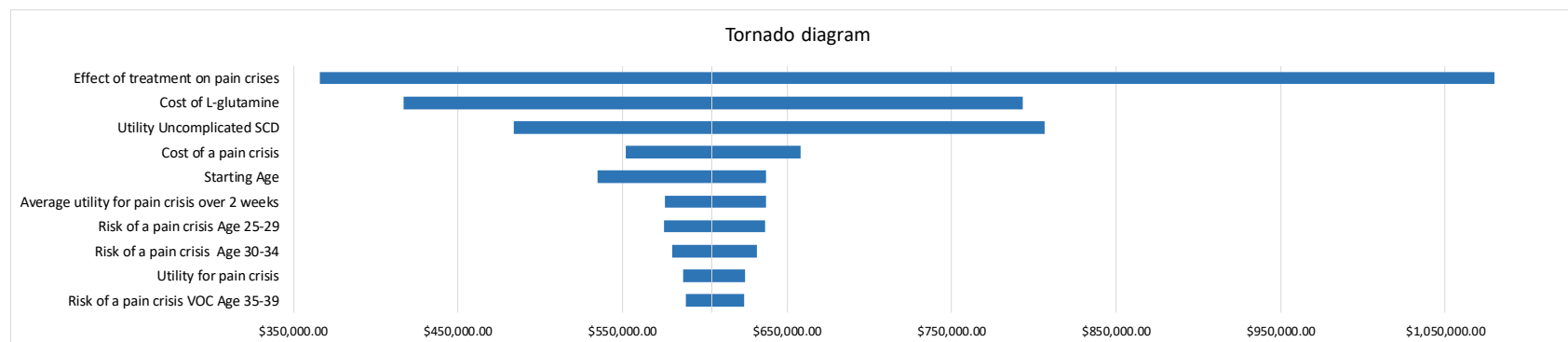
Modified Societal Perspective

Using the societal perspective, sensitivity analysis showed a similar pattern as for the health care perspective, with the cost of treatment, the utility of uncomplicated sickle cell disease, and the treatment effect on acute pain crises as the major drivers of cost per QALY for all three treatments (Figures 5.5-5.7). However, the degree of work impairment was also an important driver, especially for L-glutamine. The estimated cost per QALY did not fall below $500,000 for crizanlizumab or voxelotor across these ranges of values. However, the cost per QALY ratio for L-glutamine fell below $150,000 per QALY if assumed to have higher effectiveness or lower cost, or greater impact on work impairment.

Figure 5.5. Sensitivity Analysis of Crizanlizumab Compared to Usual Care: Modified Societal Perspective

Tornado diagram
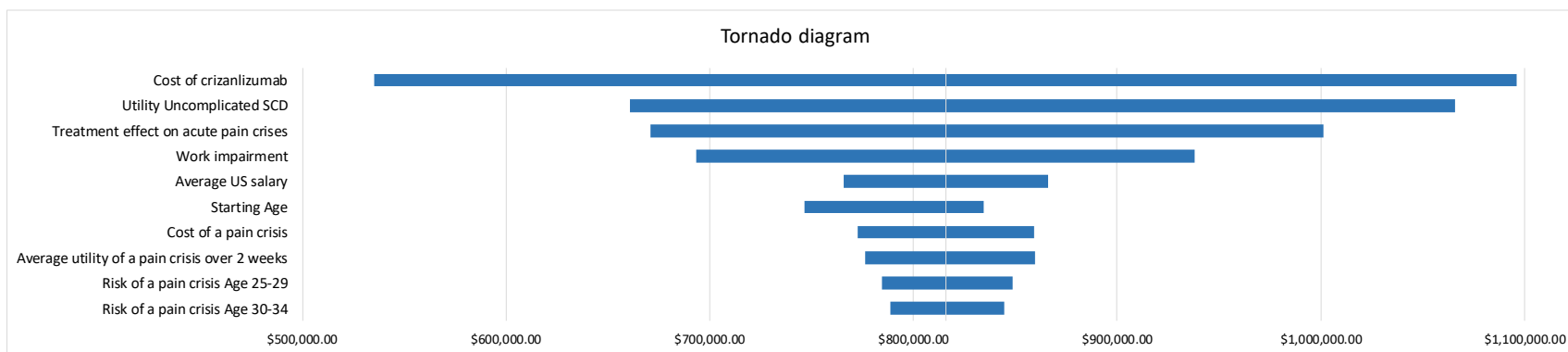
Figure 5.6. Sensitivity Analysis of Voxelotor Compared to Usual Care: Modified Societal Perspective

Tornado diagram
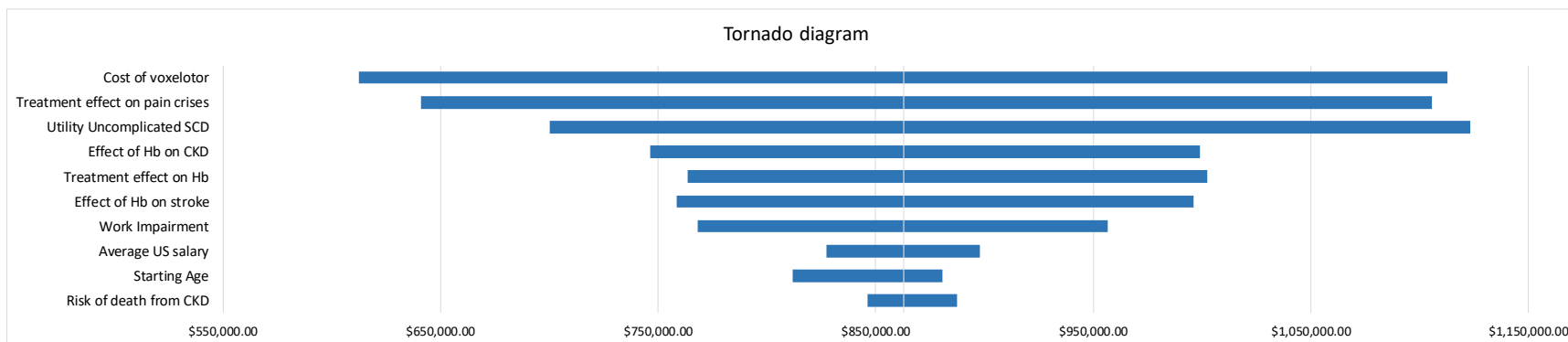
Figure 5.7. Sensitivity Analysis of L-glutamine Compared to Usual Care: Modified Societal Perspective

Tornado diagram

Effect of treatment on pain crises	
Work impairment	
Cost of L-glutamine	
Average US salary	
Utility Uncomplicated SCD	
Cost of a pain crisis	
Risk of a pain crisis Age 25-29	
Risk of a pain crisis Age 30-34	
Utility for pain crisis	
Risk of a pain crisis VOC Age 35-39	

$0.00 $100,000.00 $200,000.00 $300,000.00 $400,000.00 $500,000.00 $600,000.00
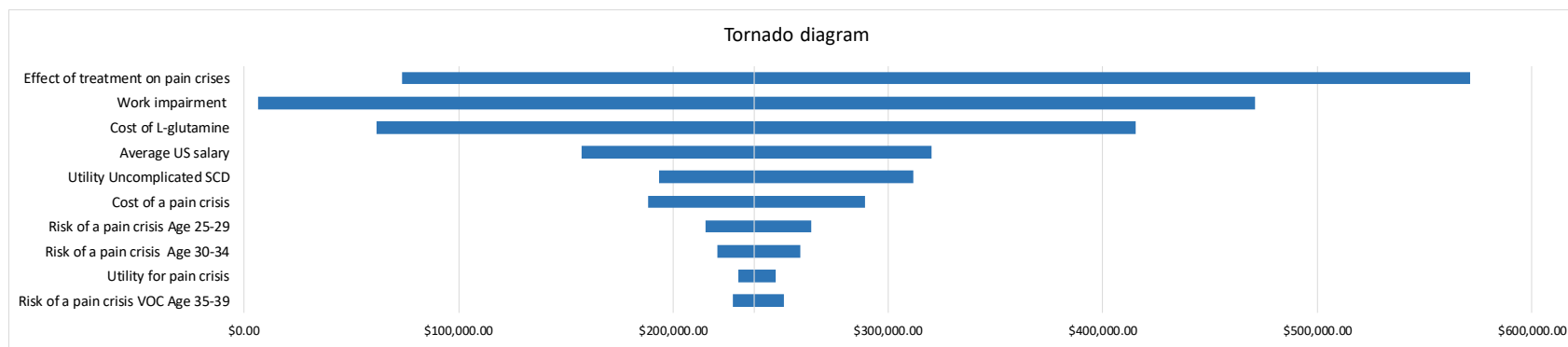
Probabilistic Sensitivity Analysis

Uncertainty was incorporated into the model estimations using probabilistic sensitivity analysis. To determine the number of simulations needed to estimate a stable estimate, we estimated the cost per QALY with 1 through 2000 simulations to determine at what point additional simulations would not affect the estimate. Analyses for all three comparisons were stable at 1000 simulations (Appendix Figure E1).

Results of the probabilistic analysis for the health care perspective are reported in Appendix Tables E6-8. These tables report the average for each output across the 1000 simulations and the 95% credible interval (i.e., the 2.5th and 97.5th percentiles). The probabilistic outputs are very similar to the deterministic outputs. The credible intervals demonstrate some large variations in the total costs, pain crises, life-years gained, evLYG and QALYs from the parameter uncertainty.

The cost-effectiveness acceptability curves (Figures 5.8-5.10) show that the probability that any of the treatments are cost-effective at generally accepted thresholds is zero. At a threshold of $1,000,000 per QALY the probability of cost-effectiveness is 0.40 for crizanlizumab, 0.97 for L-glutamine and 0.27 for voxelotor.

Figure 5.8. Cost-Effectiveness Acceptability Curve of Crizanlizumab Compared to Usual Care
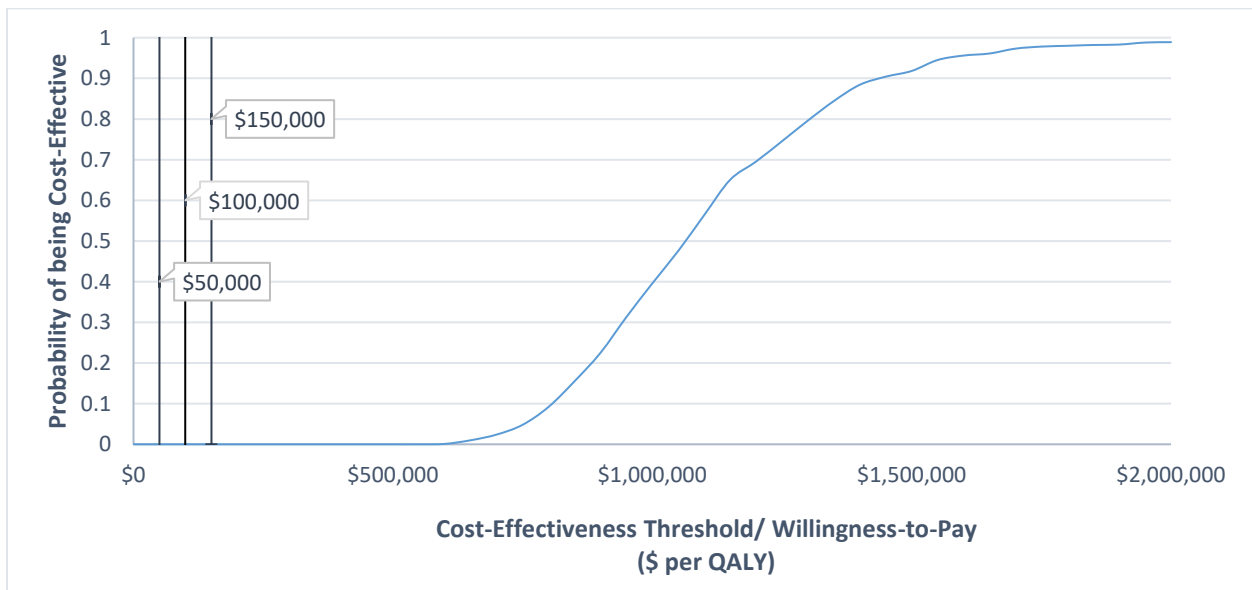
Figure 5.9. Cost-Effectiveness Acceptability Curve of Voxelotor Compared to Usual Care
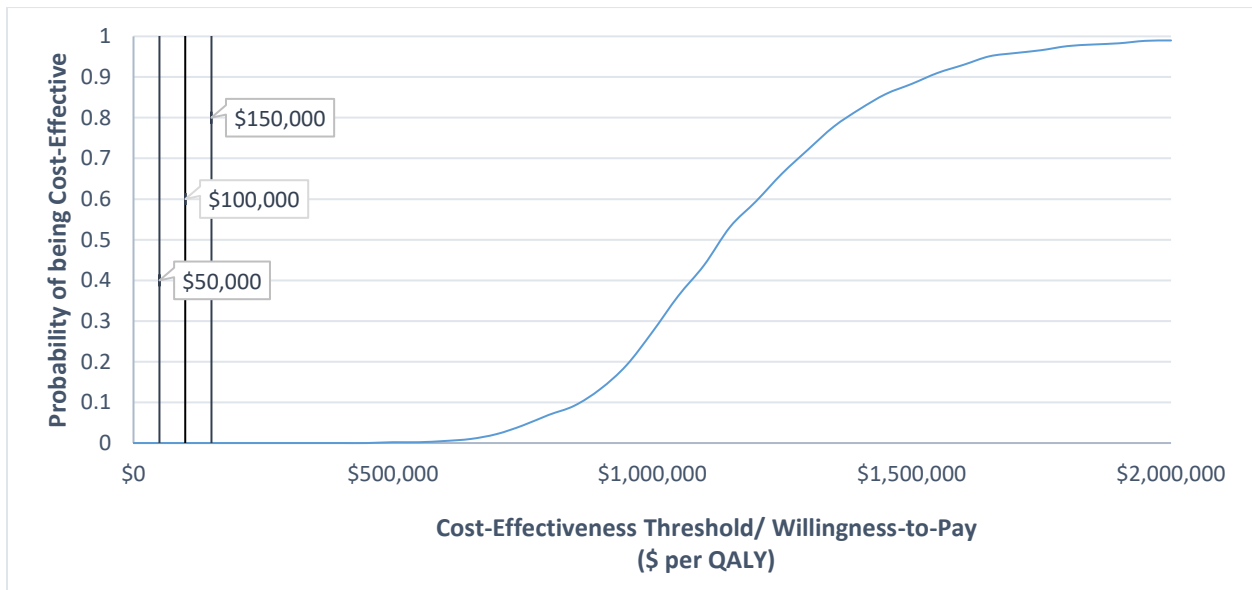
Figure 5.10. Cost-Effectiveness Acceptability Curve of L-Glutamine Compared to Usual Care
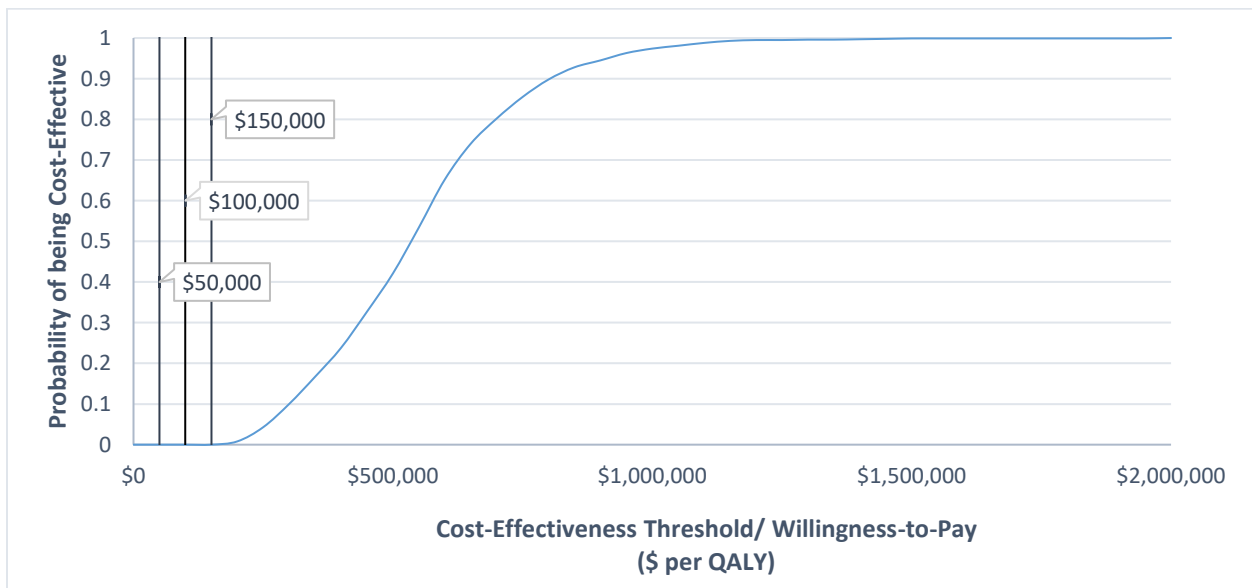
Scenario Analyses Results

Population with Higher Acute Pain Crisis Rate

Analysis of a population with 10 acute pain crises per year results in a larger difference in acute pain crises avoided and lower incremental cost-effectiveness ratios for all treatments (Tables 5.27-5.33).

Lifetime treatment costs for crizanlizumab in this population are slightly lower than in the base-case population due to the higher mortality rate resulting in a shorter length of treatment, approximately $847,000 over the lifetime, with cost-savings of approximately $330,000 from avoided acute and chronic conditions (Table 5.27). The model estimates that crizanlizumab patients will experience 78 acute pain crises over their lifetime, 42 fewer than with usual care alone. The decreased treatment costs and improved outcomes compared to the base-case result in improved incremental cost-effectiveness of crizanlizumab compared to usual care, at approximately $229,000 per LY gained, $262,000 per evLYG, and $514,000 per QALY gained. To reduce the incremental cost-effectiveness ratio to $150,000 per QALY, the baseline acute pain crisis rate would have to be 20 per year. Using the societal perspective, the incremental cost-effectiveness ratios decreased further to $185,000 per LY gained, $203,000 per evLYG and $383,000 per QALY (Table 5.28).

Table 5.27. Results for Crizanlizumab versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Health Care Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$847,000	$847,000	-	
Other Cost	$2,084,000	$1,754,000	-$330,000	-	
Total Cost	$2,084,000	$2,600,000	$516,000	-	
Acute Pain Crises	119.73	77.82	-41.91	$12,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	11.97	14.23	2.25	$229,000	per LY gained
evLYG	6.49	8.46	1.97	$262,000	per evLYG
QALYs	6.49	7.49	1.00	$514,000	per QALY gained

evLYG: equal value life years gained, **g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year**

Table 5.28. Results for Crizanlizumab versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Modified Societal Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$847,000	$847,000	-	
Other Cost	$1,718,000	$1,289,000	-$429,000	-	
Total Cost	$1,718,000	$2,136,000	$418,000	-	
VOC	119.73	77.82	-41.91	$10,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	11.97	14.23	2.25	$185,000	per LY gained
evLYG	5.16	7.22	2.06	$203,000	per evLYG
QALYs	5.16	6.25	1.09	$383,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

An additional analysis was undertaken assuming that these patients would have the same treatment effect as the subgroup of patients in the SUSTAIN trial with 5-10 pain crises in the previous year. The lower relative effect in this subgroup further decreased the ratios to $129,000 per LYG, $149,000 per evLYG and $293,000 per QALY. This scenario combined with a societal perspective resulted in $97,000 per LY gained, $108,000 per evLYG, and $204,000 per QALY (Table 5.30).

Table 5.29. Results for Crizanlizumab versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year and the Relative Treatment Effect from the Subgroup with 5-10 VOC (1.97/5.32=0.37): Health Care Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$890,000	$890,000	-	
Other Cost	$2,084,000	$1,582,000	-$502,000	-	
Total Cost	$2,084,000	$2,472,000	$387,000	-	
VOC	119.73	55.45	-64.27	$6,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Lys	11.97	14.98	3.00	$129,000	per LY gained
evLYG	6.49	9.09	2.61	$149,000	per evLYG
QALYs	6.49	7.81	1.32	$293,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.30. Results for Crizanlizumab versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year and the Relative Treatment Effect from the Subgroup with 5-10 VOC (1.97/5.32=0.37): Modified Societal Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental Cost-effectiveness Ratio	
Treatment Cost	-	$890,000	$890,000	-	
Other Cost	$1,718,000	$1,121,000	-$597,000	-	
Total Cost	$1,718,000	$2,011,000	$293,000	-	
VOC	119.73	55.45	-64.27	$5,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	11.97	14.98	3.00	$97,000	per LY gained
evLYG	5.16	7.88	2.72	$108,000	per evLY gained
QALYs	5.16	6.59	1.43	$204,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Lifetime treatment costs for voxelotor in this population with 10 acute pain crises are also lower than in the base-case population, at approximately $954,000 over the lifetime (Table 5.31). The model estimates that voxelotor patients will experience 118 acute pain crises over their lifetime, 1 fewer than with usual care. The incremental cost-effectiveness of voxelotor compared to usual care is approximately $474,000 per LY gained, $522,000 per evLYG, and $962,000 per QALY gained. There was no number of acute pain crises that would reduce the cost per QALY to $150,000. From a societal perspective, the incremental cost-effectiveness ratios decrease, but all remain over $400,000 (Table 5.32).

Table 5.31. Results for Voxelotor versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Health Care Perspective

Treatment	Usual care	Voxelotor	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$954,000	$954,000	-	
Other Cost	$2,084,000	$2,093,000	$9,000	-	
Total Cost	$2,084,000	$3,048,000	$964,000	-	
Acute Pain Crises	119.73	118.37	-1.35	$711,000	per pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$57,000	per g/dL per year
LYs	11.97	14.00	2.03	$474,000	per LY gained
evLYG	6.49	8.33	1.85	$522,000	per evLYG
QALYs	6.49	7.49	1.00	$962,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.32. Results for Voxelotor versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Modified Societal Perspective

	Usual Care	Voxelotor	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$954,000	$954,000	-	
Other Cost	$1,718,000	$1,590,000	-$128,000	-	
Total Cost	$1,718,000	$2,544,000	$826,000	-	
VOC	119.73	118.37	-1.35	$610,000	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$49,000	per g/dL per year
LYs	11.97	14.00	2.03	$407,000	per LY gained
evLYG	5.16	7.08	1.92	$430,000	per evLYG
QALYs	5.16	6.24	1.07	$769,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Lifetime treatment costs for L-glutamine in a more frequent pain crisis population are also lower than in the base-case population, approximately $255,000 over the lifetime, with cost-savings of approximately $194,000 from avoided acute and chronic conditions (Table 5.33). The model estimates that L-glutamine patients will experience 96 acute pain crises over their lifetime, 24 fewer than usual care. The incremental cost-effectiveness of L-glutamine compared to usual care is estimated as approximately $55,000 per life year gained, $61,000 per evLYG, and $122,000 per QALY gained. To reduce the incremental ratio to $150,000 per QALY, the baseline acute pain crisis rate would have to be 9.4 per year. From the societal perspective in a population with 10 acute pain crises per year, L-glutamine dominates usual care, meaning that it is less expensive, has higher LY gained, higher evLYG and higher QALYs (Table 5.34).

Table 5.33. Results for L-Glutamine versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Health Care Perspective

Treatment	Usual Care	L-glutamine	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$255,000	$255,000	-	
Other Cost	$2,084,000	$1,890,000	-$194,000	-	
Total Cost	$2,084,000	$2,146,000	$62,000	-	
Acute Pain Crises	119.73	95.51	-24.22	$3,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Lys	11.97	13.08	1.11	$55,000	per LY gained
evLYG	6.49	7.49	1.01	$61,000	per evLYG
QALYs	6.49	6.99	0.50	$122,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.34. Results for L-Glutamine versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year: Modified Societal Perspective

Treatment	Usual Care	L-Glutamine	Difference	Incremental Cost-Effectiveness Ratio
Treatment Cost	-	$164,000	$164,000	-
Other Cost	$1,718,000	$1,436,000	-$282,000	-
Total Cost	$1,718,000	$1,600,000	-$118,000	-
VOC	119.73	95.51	-24.22	Dominates
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated
LYs	11.97	13.08	1.11	Dominates
evLYG	5.16	6.22	1.05	Dominates
QALYs	5.16	5.71	0.55	Dominates

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Younger Population

Analyses of younger populations, starting treatment at 16 years old with crizanlizumab, 12 years old with voxelotor and 5 years old with L-glutamine, resulted in a slightly higher cost per QALY for crizanlizumab and voxelotor and a lower cost per QALY for L-glutamine (Tables 5.35, 5.37, 5.39). This is likely due to the lower baseline risk of acute events and chronic conditions in the younger population. This results in improvements in acute pain crises having less of an impact on acute events and chronic conditions at these younger ages.

These results suggest that 16-year-old patients who start crizanlizumab would have 32 acute pain crises over their lifetime, which is 21 acute pain crises fewer than patients on usual care alone. Lifetime cost would be approximately $1.1 million, with $154,000 cost-saving from other costs. This

results in incremental cost-effectiveness ratios of approximately $500,000 per life-year gained, $557,000 per evLYG, and $1.1 million per QALY gained. From the societal perspective, each of the incremental cost-effectiveness ratios decreased, but all remained above $400,000 (Tables 5.36).

Table 5.35. Results for Crizanlizumab versus Usual Care Alone with a Starting Age of 16 Years: Health Care Perspective

Treatment	Usual care	Crizanlizumab	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$1,135,000	$1,135,000	-	
Other Cost	$1,370,000	$1,216,000	-$154,000	-	
Total Cost	$1,370,000	$2,351,000	$980,000	-	
Acute Pain Crises	53.30	32.37	-20.93	$47,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life Years	17.77	19.73	1.96	$500,000	per LY gained
evLYG	10.45	12.21	1.76	$557,000	per evLYG
QALYs	10.45	11.31	0.86	$1,139,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.36. Results for Crizanlizumab versus Usual Care Alone with a Starting Age of 16 Years: Modified Societal Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental cost-effectiveness ratio	
Treatment Cost	-	$1,135,000	$1,135,000	-	
Other Cost	$990,000	$696,000	-$294,000	-	
Total Cost	$990,000	$1,831,000	$841,000	-	
VOC	53.30	32.37	-20.93	$40,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Lys	17.77	19.73	1.96	$429,000	per LY gained
evLYG	9.34	11.17	1.83	$459,000	per evLYG
QALYs	9.34	10.27	0.93	$903,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

This analysis suggests that 12-year-old patients who start voxelotor would have 55 acute pain crises over their lifetime, which is 4 acute pain crises fewer than patients on usual care. Lifetime cost would be $1.5 million, with $44,000 cost-saving from other costs. This results in incremental cost-effectiveness ratios of $672,000 per life-year gained, $67,000 per evLYG, and $1.2 million per QALY gained. From a societal perspective, the incremental cost-effectiveness ratios are lower, $601,000 per LY gained, $566,000 per evLYG and $951,000 per QALY (Table 5.38).

Table 5.37. Results for Voxelotor versus Usual Care Alone with a Starting Age of 12 Years: Health Care Perspective

Treatment	Usual Care	Voxelotor	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$1,460,000	$1,460,000	-	
Other Cost	$1,459,000	$1,415,000	-$44,000	-	
Total Cost	$1,459,000	$2,875,000	$1,416,000	-	
Acute Pain Crises	58.19	54.53	-3.66	$387,000	per pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$57,000	per g/dL per year
Lys	19.40	21.50	2.11	$672,000	per LY gained
evLYG	11.65	13.77	2.12	$667,000	per evLYG
QALYs	11.65	12.86	1.22	$1,162,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table 5.38. Results for Voxelotor versus Usual Care Alone with a Starting Age of 12 Years: Modified Societal Perspective

Treatment	Usual Care	Voxelotor	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$1,460,000	$1,460,000	-	
Other Cost	$1,109,000	$917,000	-$192,000	-	
Total Cost	$1,109,000	$2,377,000	$1,268,000	-	
VOC	58.19	54.53	-3.66	$346,000	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$49,000	per g/dL per year
LYs	19.40	21.50	2.11	$601,000	per LY gained
evLYG	10.61	12.84	2.24	$566,000	per evLYG
QALYs	10.61	11.94	1.33	$951,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

This analysis suggests that 5-year-old patients who start L-glutamine would have 50 acute pain crises over their lifetime, which is 16 acute pain crises fewer than patients on usual care. Lifetime treatment costs would be $334,000, with $135,000 cost-saving from other costs. This results in incremental cost-effectiveness ratios estimated to be approximately $237,000 per life-year gained, $215,000 per evLYG, and $460,000 per QALY gained. When considering a societal perspective in a starting age of 5-year olds, L-glutamine treatment results in $141,000 per LY gained, $122,000 per evLYG and $247,000 per QALY (Table 5.40).

Table 5.39. Results for L-Glutamine versus Usual Care Alone with a Starting Age of 5 Years: Health Care Perspective

Treatment	Usual care	L-Glutamine	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$334,000	$334,000	-	
Other Cost	$1,568,000	$1,433,000	-$135,000	-	
Total Cost	$1,568,000	$1,768,000	$200,000	-	
Acute Pain Crises	65.84	49.90	-15.93	$13,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life Years	21.95	22.79	0.84	$237,000	per LY gained
evLYG	13.60	14.53	0.93	$215,000	per evLYG
QALYs	13.60	14.04	0.43	$460,000	per QALY gained

Table 5.40. Results for L-Glutamine versus Usual Care Alone with a Starting Age of 5 Years: Modified Societal Perspective Treatment

Treatment	Usual Care	L-Glutamine	Difference	Incremental Cost-Effectiveness Ratio	
Treatment Cost	-	$334,000	$334,000	-	
Other Cost	$1,262,000	$1,046,000	-$216,000	-	
Total Cost	$1,262,000	$1,380,000	$118,000	-	
VOC	65.84	49.90	-15.93	$7,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	21.95	22.79	0.84	$141,000	per LY gained
evLYG	12.69	13.66	0.98	$122,000	per evLYG
QALYs	12.69	13.17	0.48	$247,000	per QALY gained

evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Threshold Analyses

The threshold analyses calculate the drug price at which each treatment would be cost-effective at different relevant thresholds, with results for the health care sector perspective shown in Table 5.41. For crizanlizumab to be cost-effective at $50,000 per QALY, the price would have to be $230 per vial or approximately $12,870 annually, and approximately $20,920 annually at $150,000 per QALY. For voxelotor to be cost-effective at $50,000 per QALY, the price would have to be $332 per package or approximately $4,050 annually, and $12,630 annually at $150,000 per QALY. L-glutamine would be cost-effective at $50,000 per QALY at $217 per package or approximately $7,910 annually, and at $11,910 annually at $150,000 per QALY.

Table 5.41. Annual Drug Costs at List and Discount Prices and at Prices at Which Each Treatment is Cost-effective at Specific Thresholds: Health Care Perspective [40]

Treatments	Input Prices		Thresholds of Interest					
	List Price	Assumed Net Price	$50K per QALY	$100K per QALY	$150K per QALY	$50K per evLYG	$100K per evLYG	$150K per evLYG
Crizanlizumab	$132,000	$96,350	$12,870	$16,890	$20,920	$17,430	$26,030	$34,620
Voxelotor	$127,000	$92,580	$4,050	$8,340	$12,630	$7,630	$15,510	$23,380
L-glutamine	$40,540	$30,050	$7,910	$9,910	$11,910	$10,380	$14,850	$19,330

evLYG: equal value life years gained, QALY: quality-adjusted life year

Using the societal perspective analysis (Table 5.42), crizanlizumab was cost-effective at $50,000 per QALY at a price of $30,580 annually, and $39,170 annually at $150,000 per QALY. Voxelotor was cost-effective at thresholds of $50,000 and $150,000 per QALY at prices of $17,460 and $26,710 annually, respectively. L-glutamine was cost-effective at thresholds of $50,000 and $150,000 per QALY at prices of $22,060 and $26,320 annually, respectively.

Table 5.42. Annual Drug Costs at List and Discount Prices and at Prices at Which Each Treatment is Cost-effective at Specific Thresholds: Modified Societal Perspective [40]

Treatments	Input Prices		Thresholds of Interest					
	List Price	Assumed Net Price	$50K per QALY	$100K per QALY	$150K per QALY	$50K per evLYG	$100K per evLYG	$150K per evLYG
Crizanlizumab	$132,000	$96,350	$30,580	$34,870	$39,170	$34,880	$43,470	$52,070
Voxelotor	$127,000	$92,580	$17,460	$22,090	$26,710	$20,720	$28,590	$36,470
L-glutamine	$40,540	$30,050	$22,060	$24,190	$26,320	$24,400	$28,870	$33,350

evLYG: equal value life years gained, QALY: quality-adjusted life year

Model Validation

Wilson-Frederick et al. examined the demographic and health utilization patterns among Medicare Fee-for-Service beneficiaries with SCD using the CMS SCD indicator. The population included 11,790 SCD patients between the ages of 18 and 75, using claims data from 2012 through 2016. In 2016, patients had an average of 7.4 emergency department visits, 3.9 days of inpatient hospitalization, and 21.1 days of outpatient utilization. Table 5.43 reports the prevalence of pulmonary hypertension, heart failure, and chronic kidney disease as reported by CMS[40] and as estimated in the model using the average age of the CMS range, as reported in the brackets. This comparison suggests that the predicted prevalence in the model is very similar to that of the Medicare population in terms of chronic disease prevalence.

Table 5.43. Comparison of Prevalence Reported in a Medicare Population Compared to Prevalence Predicted by the Model

Age range from CMS (average age used in the model)	Medicare Population	Model
		Usual Care
pHTN (%)		
18-30 (24)	35%	34%
31-45 (38)	58%	63%
46-54 (50)	75%	82%
55-64 (59.5)	87%	91%
65-75 (70)	93%	98%
HF (%)		
18-30 (24)	18%	13%
31-45 (38)	37%	35%
46-54 (50)	47%	51%
55-64 (59.5)	52%	57%
65-75 (70)	48%	55%
CKD (%)		
18-30 (24)	26%	21%
31-45 (38)	42%	39%
46-54 (50)	55%	56%
55-64 (59.5)	62%	64%
65-75 (70)	64%	69%

CKD: chronic kidney disease, CMS: Centers for Medicare and Medicaid services, HF: heart failure, pHTN: pulmonary hypertension

The national median life-expectancy for people with SCD is reported as being between 38 and 42 years old for men and between 42 and 48 years old for women.[113,115] The average patient in the usual care arm of the model is predicted to live an additional 15 years after entering the model in the base-case analysis, giving a life-expectancy of 39 years old.

The average utility for a patient with SCD on usual care was estimated to be 0.51. This is a very low health-related quality of life and reflects the very serious nature of the disease and the severity of the modelled population. For comparison, this is similar to the average score of 4.7 out of 10 that Sick Cells survey respondents rated their daily baseline pain during the past week.

Model validation suggests that the usual care population is similar to the Medicare population in terms of prevalence of chronic conditions, and has a life-expectancy similar to that reported in the literature.

Limitations

To simplify the model, it was assumed that only one chronic condition and one acute condition could occur each cycle. This creates a situation where chronic conditions and acute conditions become competing events. Therefore, by decreasing one event in the model it allows other events to occur more frequently. To correct for the competing events, the model was calibrated to minimize the difference in the number of acute events and chronic conditions because of the reduction in acute pain crises in the treatment arm. The specific steps we followed to perform this calibration are described in Appendix E. This method can be validated by investigating how the model predicts acute and chronic conditions compared to known SCD populations, as was done in the validation section above.

The event rates used in the model are from claims data. This has the potential to underestimate event rates, particularly those that do not result in hospitalization. However, claims data is expected to capture the most debilitating and costly events. Event rates were also tested in sensitivity analysis. In addition, the results used for many of the indirect cost estimates in the societal perspective analysis came from a web-based survey of sickle cell patients and their caregivers, and may not be representative of the overall sickle cell population in the US.

Due to the lack of published evidence, a number of assumptions had to be made. These include: the risk effects of acute pain crisis on AKI/renal infarction, the prevalence of opioid tolerance and dependence, the risk factors of myocardial infarction and heart failure on death, and the disutility of AKI/renal infarction and pulmonary hypertension in the SCD population. In addition, a number of assumptions had to be made about how to combine risk factors and dis-utilities for patients experiencing multiple acute and chronic conditions. These assumptions were described previously and the rationale described.

This model focuses on improvements in health states and the quality-of-life and length-of-life from these improvements. The use of other quality of life metrics or values from different populations could yield different QALY estimates than those reported here. In addition, SCD often has a broad and deep impact on patients' psychosocial well-being. Some of these impacts are captured in measures of quality-of-life, such as anxiety and depression, the ability to take care of one's self, and to perform activities of usual care. Further improvements from treatments for SCD may occur in aspects that are not captured within the model; these potential other benefits are discussed in later sections, along with other contextual considerations.

Conclusions

The prevalence rates predicted in the model suggest a cohort similar to Medicare FFS patients with SCD. Reduction in acute pain crises and improvement in hemoglobin both result in fewer acute events and a lower prevalence of chronic conditions. These improvements extend life expectancy

and lead to an improvement in health-related quality of life. The lifetime total (discounted) cost of a 24-year-old patient on usual care is $1.1 million. The life-time treatment cost of crizanlizumab is $970,000, voxelotor is $1.1 million and L-glutamine costs approximately $299,000.

Crizanlizumab treatment resulted in the fewest acute pain crises, with 27 over the patient's life compared to 43 for patients on usual care, 42 for patients on voxelotor, and 34 for patients on L-glutamine. Voxelotor treatment resulted in the lowest rate of stroke, with a mean of 0.37 over the patient's lifetime compared to 0.59 for patients on usual care,0.57 for patients on L-glutamine, and 0.56 for patients on crizanlizumab. There was very little difference in the prevalence of chronic conditions with crizanlizumab and L-glutamine, with treatments causing slightly higher prevalence in some age groups due to lower mortality on treatment. However, treatment with voxelotor resulted in lower prevalence of pulmonary hypertension and chronic kidney disease. All treatments resulted in higher life expectancy than usual care alone.

In the base case, cost per QALY estimates range from $604,000-1.1 million, while cost per life-years gained and cost per evLYG ranged from $238,000 to $549,000 and $270,000 to $589,000, respectively. For a population with 10 pain crises per year L-glutamine was cost-effective at a threshold of $150,000 per QALY and crizanlizumab was cost-effective at a threshold of $150,000 per evLYG using the efficacy data for the 5-10 pain crises subgroup. Using the societal perspective L-glutamine was cost-effective at a threshold of $150,000 per evLYG.

Disparities

It is important to note that economic models such as this one cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations such as patients with SCD. It is also unclear what impact treatments for these populations will have on those systemic issues, or vice versa. For example, the majority of people with SCD in the US have African American heritage. Life expectancy at birth is 4.442% lower for blacks than for whites in the US (75.3 years vs. 78.8 years).[41] In an exploratory analysis, we estimated that if all people with SCD were treated with crizanlizumab and all were assumed to be African-American, the increase in life years would decrease the overall disparity in life expectancy by a relative 3.6% (i.e., to 4.426% lower rather than 4.442%).

As an example of these systemic issues, we compared the life expectancy of patients with SCD in our model to the life expectancy of a matched non-SCD population and to the general US population (Figure 5.11). The estimate of life expectancy for the matched non-SCD cohort was obtained from an analysis by Lubeck et al.[42], which developed a non-SCD population cohort that matched the age, sex, and race/ethnicity of the SCD population. Lubeck et al. reported a similar 3-year difference in life expectancy between the US population and the matched non-SCD cohort as seen above. Our model estimated life expectancy for SCD patients as approximately 43.5 years (undiscounted), reflecting a 45% decrement from the general US life expectancy of 79 years.

Treatment with crizanlizumab or voxelotor was estimated in the model to add approximately 4 undiscounted years to life expectancy for treated SCD patients, reducing the disparity from 45% to 40% compared to the general population. Treatment with L-glutamine was estimated to add approximately 1.9 years (undiscounted) to life expectancy for treated SCD patients, reducing the disparity to 42.5% compared to the general population.

Figure 5.11. Comparison of Life Expectancy for People with Sickle Cell Disease (with and without Treatment) to Matched Non-Sickle Cell Disease and General US Populations

LE: life expectancy, SCD: sickle cell disease

Given the severe impact of this condition on people with sickle cell disease, on top of the racial disparities in health care faced by most of these patients, decision-makers in the US may wish to consider giving special weighting to other benefits and to contextual considerations that would lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

5.4 Summary and Comment

As discussed above, the model made a number of assumptions favorable to all the medications, but particularly to voxelotor given the lack of evidence that voxelotor actually reduces events or the need for transfusion. In the case of L-glutamine, we had concerns about the validity of the results from the clinical trials given differential dropout rates. The report concluded above that the evidence for net benefit was less conclusive for L-glutamine and voxelotor than for crizanlizumab, and that should be kept in mind when interpreting the results discussed below, which use point estimates of benefit that have more or less uncertainty for the various therapies.

Treatment costs were the main driver of the cost-effectiveness results, with average annual costs (after accounting for discontinuation) of approximately $79,000 for crizanlizumab, $78,000 for voxelotor and $24,000 for L-glutamine using net prices. Combined with relatively small improvements in QALYs gained, incremental cost-effectiveness ratios ranged from $604,000 to $1.1 million per QALY using a health care sector perspective. Using a societal perspective including productivity gains and other indirect costs, incremental ratios were lower but still above $150,000 per QALY, ranging from $289,000 for L-glutamine to $866,000 per QALY for voxelotor. None of the scenario analyses undertaken lowered the estimated cost per QALY of crizanlizumab or voxelotor to less than $150,000 per QALY from a health care sector or societal perspective, although scenario analyses suggest treatment is most cost-effective for patients with higher rates of acute pain crises. Patients who experience 10 acute pain crises per year may have a cost per QALY as low as $144,000 with L-glutamine.

Although a reduction in acute pain crises and increase in hemoglobin will provide relief to patients, they will continue to suffer from other acute and chronic conditions that will have a significant impact on their quality of life. The impact of these therapies on these other acute and chronic conditions has yet to be demonstrated in clinical trials, although we made assumptions that included impacts of these treatments on several of these conditions. As a result, there is currently a large difference in the cost per QALY and the cost per life-year and evLYG. For example, cost per evLYG ranged from approximately $270,000 for L-glutamine to $589,000 for voxelotor from the health care perspective, and from $134,000 per evLYG for L-glutamine to $488,000 per evLYG for voxelotor. Patients who experience 10 acute pain crises per year may have a cost per evLYG below $150,000 with crizanlizumab or L-glutamine.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness or cost-effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that should influence the judgment of policymakers in their determination of the relative value of different interventions. Specific potential other benefits and contextual considerations that we evaluate for each intervention are listed in Table 6.1 below, and the subsequent text provides detail about the elements that are applicable to the comparison of crizanlizumab, voxelotor, and L-glutamine to optimal usual care. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to optimal usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to optimal usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

6.1 Potential Other Benefits

As noted in the Introduction and section on Patient Perspectives, the way patients with SCD have been treated in the US is a tragedy that has extended over many decades. Patients and their families have experienced neglect, racism, and total disregard. Research into treatment improvements has received less funding than many other conditions that affect fewer patients. The overall "system" of health insurance and care has betrayed the SCD community.

The potential other benefits of effective treatments for SCD therefore are highly relevant. It is clear that treatment with new therapies may reduce important health disparities that exist across racial and socio-economic groups in the US. Specifically, effective treatment could potentially reduce the gap in life expectancy between black and white Americans and between the poor and rich in the US. Further, if these new therapies can be shown to directly impact other acute and chronic morbidities outside of those measured in the current clinical trials, patients could experience significant improvements in their quality of life.

It also seems likely that new, effective treatments could reduce caregiver burden. Questions will remain about whether the magnitude of the clinical benefits seen in the early trials of the drugs under review will reach the threshold of having a noticeable effect on caregivers, but if patients have less pain, suffer fewer morbidities, have fewer hospitalizations, and need fewer doctor visits, then their families and caregivers would have more time to focus on their own education, careers, family, friends, and other interests. Improvement in caregivers' quality of life can have a rebound positive effect for the patient, improving further their own mental, emotional, and physical health.

Similarly, effective treatment could increase the chances for employment among patients with SCD and improve the productivity of all patients, whether they are working or performing family and community functions.

Crizanlizumab, voxelotor, and L-glutamine all have different mechanisms of action both from each other and from hydroxyurea. This is a significant step forward in the field of SCD. Patients who have not been able to tolerate hydroxyurea now have other treatment options. Equally important all three products have different mechanisms of action and work on different critical pathways that underlie the different phenotypic expressions of the disease. This now provides novel treatment options that can be tailored to the different phenotypes of the disease; options to provide a more targeted approach that have not been available before. It also provides an opportunity to potentially combine therapies to address multiple pathophysiological pathways as opposed to just one. While there is much to be learned about the potential benefits and harms of combination therapy, there remains significant potential for new understanding and hope for additive health benefit for patients. With these new treatment options, a more targeted approach, and the potential to deploy multiple concurrent therapies, comes the potential for a healthier patient.

By providing a more hopeful outcome for patients these new treatments may improve the attractiveness of SCD care for clinicians, leading to a new influx of talent and resources. The terrible dysfunction and lack of coordination between the pediatric care of SCD patients and adult care may receive new focus and be subject to innovative care delivery changes. Thus, a suite of new treatments for SCD may have the potential to kickstart a long overdue revolution in the care of the total patient and family from diagnosis throughout the lifespan.

6.2 Contextual Considerations

As with potential other benefits, the contextual considerations related to SCD are significant. SCD is a condition that has both many acute, severe effects, and a litany of substantial negative effects throughout patients' shortened lifespans. Individuals with SCD have an extremely high burden of disease that significantly impacts both their quality of life and length of life. Patients experience tremendous physical pain beginning in the first year of life, progress to organ damage in childhood, organ failure in their teens, twenties, and thirties and early death. In the US, this high disease burden is made worse by racism and bias resulting in poor access to care and substandard care

when they do attempt to find help through the healthcare system. They find themselves in financial difficulty due to their disease, have difficulty accessing care because there are so few specialists trained to care for them, and when they do access care are often treated like drug addicts left to suffer agonizing pain, even within hospital wards and emergency rooms, without relief.

The care they receive is further compromised due to historic disparities in research funding. Funding for research into treatments for SCD has been far less than for other diseases more commonly occurring in Caucasian populations. As a result, if a patient is able to find a hematologist who treats SCD, they have historically had few treatment options: bone marrow transplant, hydroxyurea, chronic transfusion, all at significant cost, some with significant risk, and/or side effects. These new therapies are the first in many years to offer new mechanisms of action and new hope for less pain and suffering.

Finally and not surprisingly, their very complex disease becomes further complicated by the added psychological and emotional toll of having to endure, interact with, and attempt to navigate a broken, dysfunctional, and dispassionate health care system. This is the context in which patients, their families, loved ones, and the few committed health care providers who care for them find themselves in the current landscape of SCD care. There is hope that these new therapies may mark the beginning of a new context, a new landscape, a new excitement, and a new path forward for patients, their caregivers, and their loved ones.

7. Health Benefit Price Benchmarks

Health Care Perspective

Annual health benefit price benchmarks (HBPBs) of crizanlizumab, voxelotor, and L-glutamine using the health care sector perspective are presented in Table 7.1, with corresponding per-unit prices shown in Table 7.2. The health benefit benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY (or evLYG) gained. For crizanlizumab, price discounts of approximately 84% to 87% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For voxelotor, prices approximately 90% to 93% below WAC would achieve $100,000 to $150,000 per QALY threshold prices. For L-glutamine, prices approximately 71% to 76% below WAC would achieve $100,000 to $150,000 per QALY threshold prices.

Table 7.1. Annual Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine: Health Care Perspective

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
QALYs Gained	$132,000	$16,890	$20,920	84% to 87%
evLYG		$26,030	$34,620	74% to 80%
Voxelotor				
QALYs Gained	$127,000	$8,340	$12,630	90% to 93%
evLYG		$15,510	$23,380	82% to 88%
L-glutamine				
QALYs Gained	$40,540	$9,910	$11,910	71% to 76%
evLYG		$14,850	$19,330	52% to 63%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

We are including results for price per evLYG to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which crizanlizumab meets the $100,000 to $150,000 per evLYG range for use in these patients would require a 74% to 80% discount. For voxelotor, the relevant cost per evLYG price range would require 82% to 88% discounts for the $100,000 to $150,000 per evLYG thresholds. For L-glutamine, the relevant cost per evLYG price range requires 52% to 63% discounts to reach the $100,000 to $150,000 per evLYG thresholds. The cost per evLYG price ranges are higher than the cost per QALY range for all three of these drugs. This is because each of these treatments is estimated to result in higher evLYG than QALYs gained, reflecting the low quality of life for many

patients with sickle cell disease during later years and the potential for these treatments to increase the life expectancy of patients with sickle cell disease.

Table 7.2. Per-Unit Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine: Health Care Perspective

Annual Prices Using…	WAC/Unit	Price/Unit at $100,000 Threshold	Price/Unit at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
QALYs Gained	$2,360	$300	$370	84% to 87%
evLYG		$470	$620	74% to 80%
Voxelotor				
QALYs Gained	$10,420	$690	$1,040	90% to 93%
evLYG		$1,270	$1,920	82% to 88%
L-glutamine				
QALYs Gained	$1,110	$270	$330	71% to 76%
evLYG		$410	$530	52% to 63%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

Modified Societal Perspective

Annual health benefit price benchmarks (HBPBs) of crizanlizumab, voxelotor, and L-glutamine using the modified societal perspective are presented in Table 7.3, with corresponding per-unit prices shown in Table 7.4. For crizanlizumab, price discounts of approximately 70% to 74% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For voxelotor, prices approximately 79% to 83% below WAC would achieve $100,000 to $150,000 per QALY threshold prices. For L-glutamine, prices approximately 35% to 40% below WAC would achieve $100,000 to $150,000 per QALY threshold prices.

Table 7.3. Annual Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine: Modified Societal Perspective

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
Per QALY Gained	$132,000	$34,870	$39,170	70% to 74%
Per evLYG		$43,470	$52,070	61% to 67%
Voxelotor				
Per QALY Gained	$127,000	$22,100	$26,710	79% to 83%
Per evLYG		$28,590	$36,470	71% to 77%
L-glutamine				
Per QALY Gained	$40,540	$24,190	$26,320	35% to 40%
Per evLYG		$28,870	$33,350	18% to 29%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

The annual price at which crizanlizumab meets the $100,000 to $150,000 per evLYG range for use in these patients would require a 61% to 67% discount. For voxelotor, the relevant cost per evLYG price range would require 71% to 77% discounts for the $100,000 to $150,000 per evLYG thresholds. For L-glutamine, the relevant cost per evLYG price range requires only 18% to 29% discounts to reach the $100,000 to $150,000 per evLYG thresholds. As was seen with the health care perspective results, the cost per evLYG price ranges are higher than the cost per QALY range for all three of these drugs when using the societal perspective.

Table 7.4. Per-Unit Health Benefit Price Benchmarks for Crizanlizumab, Voxelotor, and L-Glutamine: Modified Societal Perspective

	WAC/Unit	Price/Unit at $100,000 Threshold	Price/Unit at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Crizanlizumab				
Per QALY Gained	$2,360	$620	$700	70% to 74%
Per evLYG		$780	$930	61% to 67%
Voxelotor				
Per QALY Gained	$10,420	$1,810	$2,190	79% to 83%
Per evLYG		$2,350	$3,000	71% to 77%
L-glutamine				
Per QALY Gained	$1,110	$660	$720	35% to 41%
Per evLYG		$790	$910	18% to 29%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

8. Potential Budget Impact

8.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of each recently approved drug (crizanlizumab and voxelotor) for prevalent individuals in the United States (US) with SCD. (L-glutamine was not included in this analysis because of its established presence in the market and inclusion in current health care budgets.) Following the FDA label indications, we restricted the prevalent SCD population to adults and pediatric patients aged 16 years and older for crizanlizumab and to adults and pediatric patients aged 12 years and older for voxelotor. In our estimates of potential budget impact, we used the wholesale acquisition costs (WAC), assumed net prices, and the $50,000, $100,000, and $150,000 cost-effectiveness threshold prices for each drug.

8.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis includes the estimated number of individuals with SCD in the US who would be eligible for treatment with each drug. To estimate the size of the potential candidate population for treatment, we first used an estimate from Hassell et al., who used 2008 US Census data and birth-cohort screening prevalence data to obtain a prevalence of approximately 98,000 individuals with SCD in the US.[2] We applied the calculated 2008 prevalence rate to the average 2020-2024 estimated US population to arrive at an eligible population size of approximately 109,000 individuals with SCD. When applied to the population aged 16 years and older, this results in an estimate of approximately 87,500 patients eligible for treatment with crizanlizumab, or approximately 17,500 patients each year over five years. When applied to the population aged 12 years and older, this results in an estimate of approximately 93,000 patients eligible for treatment with voxelotor, or approximately 18,600 patients each year over five years. We assumed that all SCD patients meeting the age criterion would be eligible for each treatment, and that each drug would be added to usual care rather than displacing other treatments.

ICER's methods for estimating potential budget impact are described in detail elsewhere[144] and have been recently [updated]. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a

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potential budget impact threshold that is aligned with overall growth in the U.S. economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

Table 8.1 illustrates the five-year annualized per-patient potential budget impact of crizanlizumab compared to usual care in this population. These results are based on the WAC list price ($131,992 per year), the net price ($96,354), and the annual threshold prices for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care (approximately $20,920, $16,890, and $12,870, respectively).

Table 8.1. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Crizanlizumab Plus Usual Care versus Usual Care Alone

	Average Annual Per Patient Budget Impact				
	At WAC	At Net Price*	At $150,000/QALY Price	At $100,000/QALY Price	At $50,000/QALY Price
Crizanlizumab	$148,600	$124,000	$72,000	$69,300	$66,500
Usual Care	$70,600				
Net Impact	$78,000	$53,400	$1,400	-$1,400	-$4,100

*Assumed 27% discount.
All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
QALY: quality-adjusted life year

For crizanlizumab, the average annualized potential budgetary impact when using its WAC was an additional per-patient cost of approximately $78,000 versus usual care, and approximately $53,400 at its assumed net price. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from cost-saving to approximately $1,400 per patient over this time horizon.

The potential budget impact analysis showed cost-savings in the first five years for crizanlizumab at the $100,000 and $50,000 per QALY threshold prices. The prices at different cost-effectiveness thresholds are calculated over the lifetime of the model, while the potential budget impact analysis focuses on the first five years of treatment. In this case, most cost offsets occur early on, as treatment delays development of chronic conditions relative to usual care. Therefore, at the threshold prices, potential budget impact could be cost saving in the short term. As patients eventually develop more chronic conditions, the remaining impact of treatment is mainly on acute events; this leads to decreases in cost offsets while the treatment cost remains relatively constant, resulting in higher (positive) net costs in later years (following year 12).

In the population eligible for crizanlizumab, as shown in Figure 8.1, approximately 21% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at crizanlizumab's WAC. Approximately 31% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. All eligible patients could be treated at the $150,000, $100,000 and $50,000 threshold prices, with estimated potential budget impact of approximately 8% of the threshold at the $150,000 threshold price and cost savings at the $100,000 and $50,000 threshold prices.

Figure 8.1. Potential Budget Impact Scenarios of Crizanlizumab Plus Usual Care vs. Usual Care Alone at Different Acquisition Prices*

 *Net prices based on assumed 27% discount.
BI: budget impact, QALY: quality-adjusted life year

Table 8.2 illustrates the five-year annualized per-patient potential budget impact of voxelotor plus usual care compared to usual care in the voxelotor-eligible population. These results are based on the WAC ($126,827 per year), the assumed net price ($92,584 per year), and the annual threshold prices for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care (approximately $12,630, $8,340, and $4,050, respectively).

Table 8.2. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Voxelotor Plus Usual Care versus Usual Care Alone

	Average Annual Per Patient Budget Impact				
	At WAC	**At Net Price***	**At $150,000/QALY Price**	**At $100,000/QALY Price**	**At $50,000/QALY Price**
Voxelotor	$169,800	$136,200	$74,200	$70,900	$67,600
Usual Care	$70,600				
Net Impact	$92,200	$65,600	$3,600	$280	-$3,000

*Assumed 27% discount.
All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
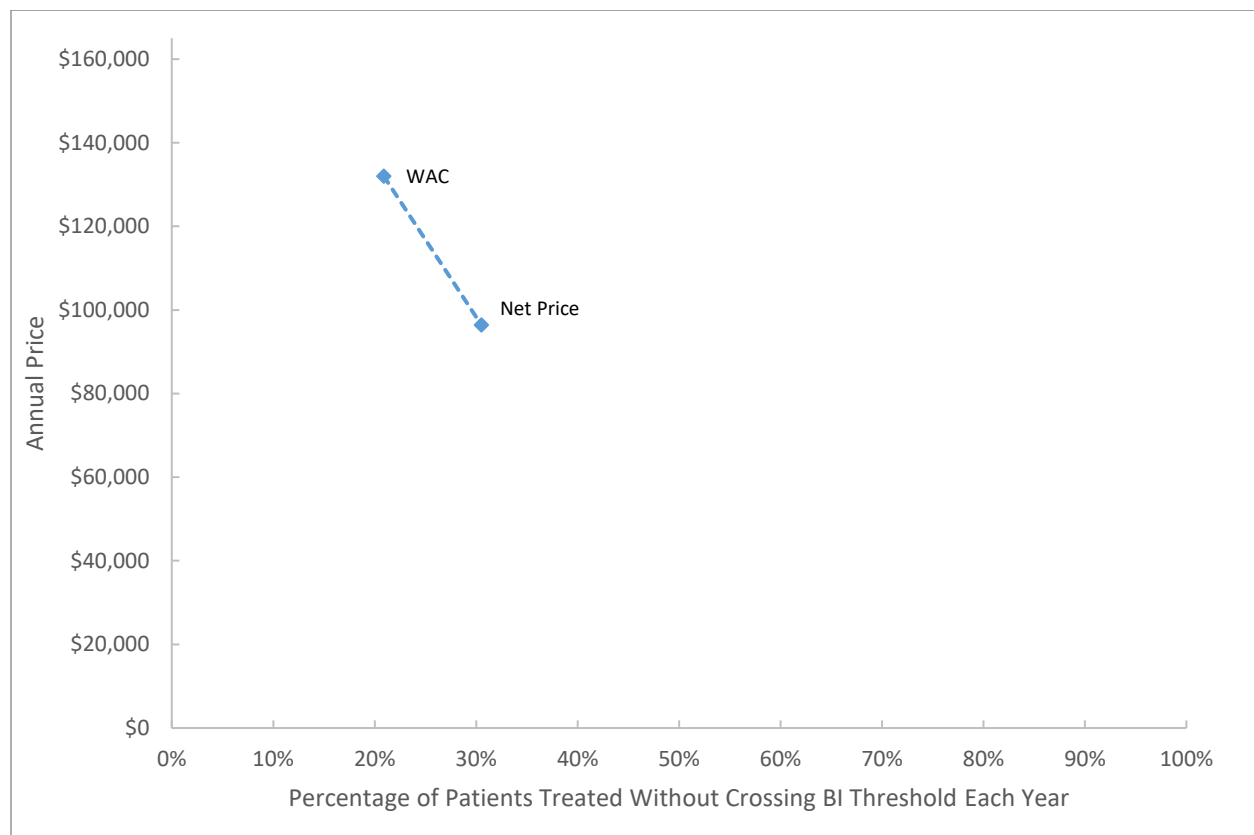QALY: quality-adjusted life year

For voxelotor, the average annualized potential budgetary impact when using its WAC was an additional per-patient cost of approximately $92,200 versus usual care, and approximately $65,600 at its assumed net price. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from cost-saving to approximately $3,600per patient over this time horizon.

As shown in Figure 8.2, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at voxelotor's list price (WAC). Approximately 23% of eligible patients could be treated without crossing the budget impact threshold at the assumed net price. All eligible patients could be treated at the $150,000, $100,000 and $50,000 threshold prices, with estimated potential budget impact of approximately 24% of the threshold at the $150,000 threshold price, 2% of the threshold at the $100,000 threshold price, and cost savings at the $50,000 threshold price.

Figure 8.2. Potential Budget Impact Scenarios of Voxelotor Plus Usual Care vs. Usual Care Alone at Different Acquisition Prices*
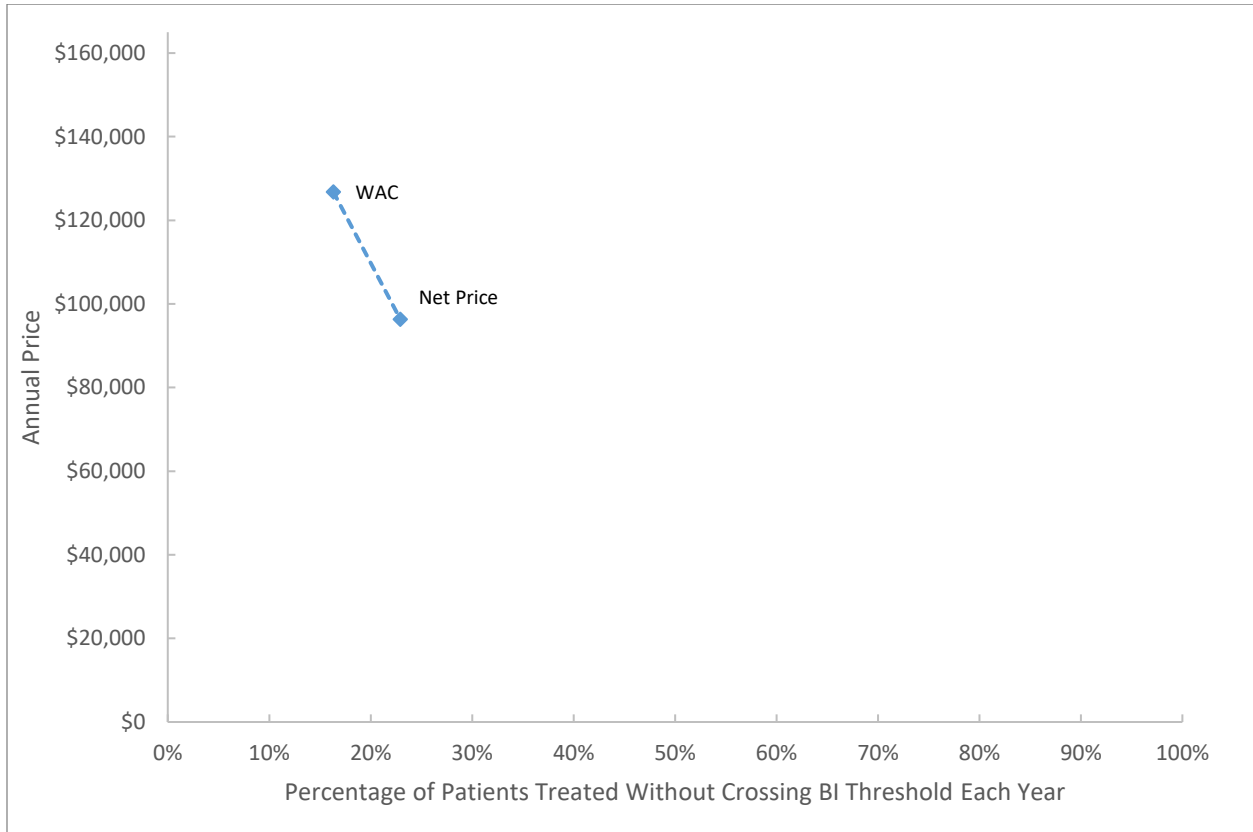
*Net prices based on assumed 27% discount.
BI: budget impact, QALY: quality-adjusted life year

The potential budget impact analysis showed cost-savings in the first five years for voxelotor at the $50,000 per QALY threshold prices. As was the case with crizanlizumab, most cost offsets occur early on, as treatment delays development of chronic conditions relative to usual care. For the $50,000 per QALY threshold price, potential budget impact could be cost saving in the short term. As patients eventually develop more chronic conditions, the remaining impact of treatment is mainly on acute events; this leads to decreases in cost offsets while the treatment cost remains relatively constant, resulting in positive net costs in later years.

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This is the first ICER review of SCD.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies for Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

#	
1	exp anemia, sickle cell/
2	((sickle adj3 (disease or an?emia)) or 'sickle cell' or meniscocyt* or drepanocyte* or sickl* or (SC adj3 (disease or an?emia))).ti,ab.
3	hemoglobin, sickle/ or (h?emoglobin adj5 sickl*).ti,ab.
4	((h?emoglobin or hb or hb- or hgb) adj3 (SS or S-S or SC or S-C or SB* or b0 or S-beta or thalassemia or beta-zero or beta plus)).ti,ab.
5	(glutamine or l-glutamine).ti,ab
6	(endari or xyndari).ti,ab
7	(crizanlizumab or seg101 or selg1).ti,ab
8	(voxelotor or gbt440).ti,ab
9	Or/6-8
10	Or/1-4
11	10 and 5
12	9 or 11
13	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
14	12 not 13
15	Animals.sh
16	Humans.sh
17	15 or (15 and 16)
18	14 not 17
19	Limit 18 to English Language
20	Remove duplicates from 19

Table A3. Search Strategy for EMBASE

#1	'sickle cell anemia'/exp
#2	((sickle NEAR/3 (disease OR an*emia)):ti,ab) OR 'sickle cell':ti,ab OR meniscocyt*:ti,ab OR drepanocyte*:ti,ab OR sickl*:ti,ab OR ((sc NEAR/3 (disease OR an*emia)):ti,ab)
#3	'hemoglobin s'/exp OR ((h?emoglobin NEAR/5 sickl*):ti,ab)
#4	(h?emoglobin OR hb OR 'hb-' OR hgb) NEAR/3 (ss OR 's-s' OR sc OR 's-c' OR 'sb' OR b0 OR 's-beta' OR thalassemia OR 'beta-zero' OR 'beta plus')
#5	'glutamine'/mj OR glutamine:ti,ab OR 'l-glutamine':ti,ab
#6	endari:ti,ab OR xyndari:ti,ab
#7	'crizanlizumab' OR seg101:ti,ab OR selg1:ti,ab
#8	'voxelotor' OR gbt440:ti,ab
#9	#1 OR #2 OR #3 OR #4
#10	#6 OR #7 OR #8
#11	#5 AND #9
#12	#10 OR #11
#13	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#14	#12 NOT #13
#15	#14 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#16	#15 AND [english]/lim
#17	#16 AND [medline]/lim
#18	#16 NOT #17

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Sickle Cell Disease

```
┌─────────────────────────┐   ┌─────────────────────────┐
│ 96 references identified │   │ 0 references identified  │
│ through literature search│   │ through other sources    │
└─────────────────────────┘   └─────────────────────────┘
              │                            │
              └──────────────┬─────────────┘
                             ▼
              ┌─────────────────────────┐
              │ 96 references after      │
              │ duplicate removal        │
              └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────────────┐        ┌─────────────────────────┐
              │ 96 references screened   │───────▶│ 70 citations excluded    │
              └─────────────────────────┘        └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────────────┐        ┌─────────────────────────┐
              │ 26 references assessed for│──────▶│ 15 citations excluded    │
              │ eligibility in full text  │       │ 2 Population             │
              └─────────────────────────┘        │ 1 Intervention           │
                             │                    │ 4 Study Design           │
                             ▼                    │ 8 Other                  │
              ┌─────────────────────────┐        └─────────────────────────┘
              │ 11 total references      │
              │    3 RCTs                │
              └─────────────────────────┘
```
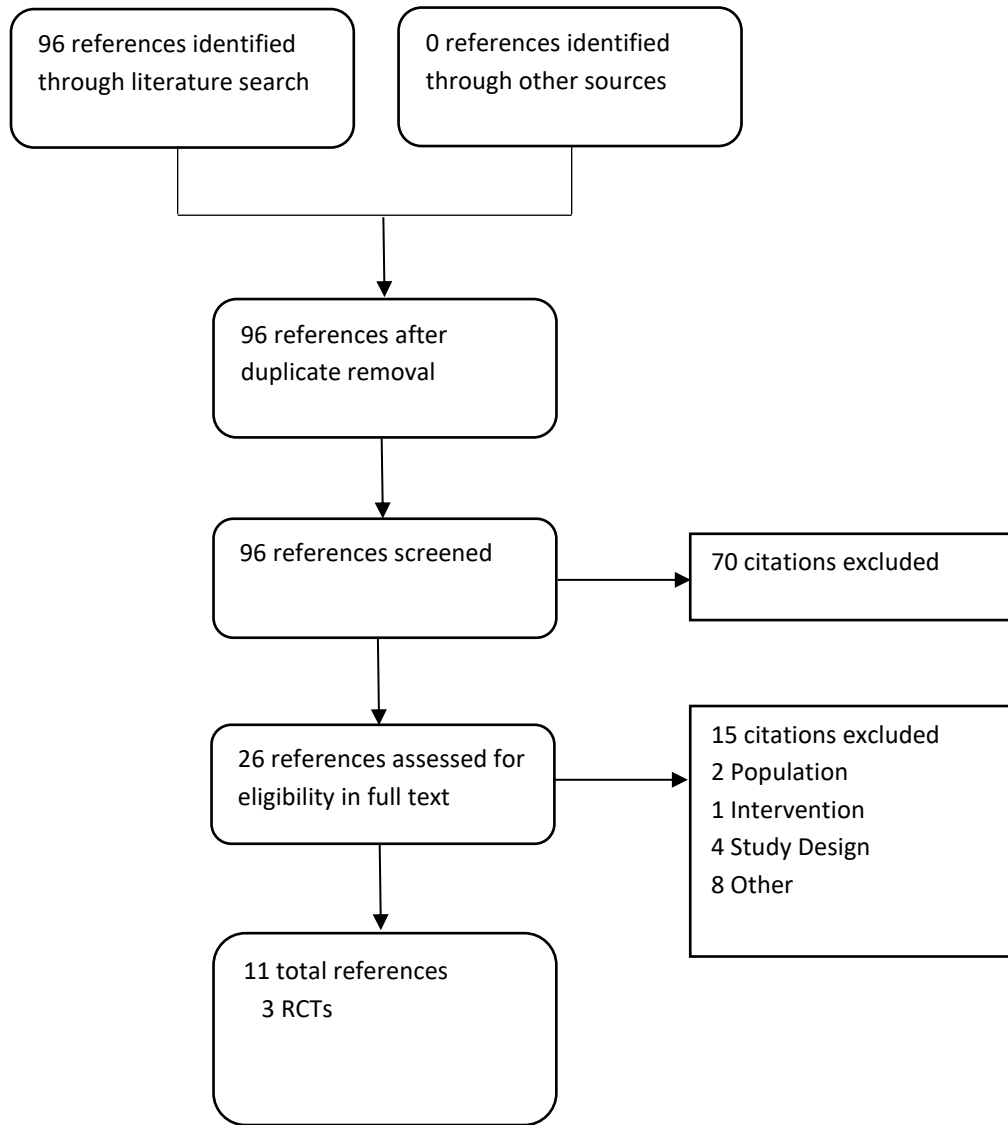
Appendix B. Previous Systematic Reviews and Technology Assessments

[NICE: Crizanlizumab for preventing sickle cell crises in sickle cell disease (ID1406], Expected publication date: 24 March 2021](#)

NICE is currently evaluating the clinical and cost effectiveness of crizanlizumab within its marketing authorization for preventing sickle cell disease. Proposed comparators include established clinical management without crizanlizumab including: hydroxycarbamide, blood transfusions, allogenic stem cell transplants, or optimal supportive care. Outcomes of interest being evaluated include mortality, number and severity of sickle cell crises, recurrent events, complications of SCD (stroke, acute chest syndrome, organ damage), adverse events, and health related quality of life outcomes.

[NICE: Voxelotor for treating sickle cell disease [ID1403], Expected publication date: TBC](#)

NICE is currently evaluating the clinical and economic effectiveness of voxelotor for the treatment of sickle cell disease.

Hutcherson et al. (2019). "Systematic Review of L-Glutamine for Prevention of Vaso-Occlusive Pain Crisis in Patients with Sickle Cell Disease".[145]

Investigators conducted a systematic review to evaluate the safety and efficacy of L-glutamine to prevent vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD). Select inclusion and exclusion criteria used to identify studies included randomized-controlled trials, observational studies, or case studies in patients with sickle cell disease, sickle cell anemia, or thalassemia taking l-glutamine. Studies were excluded if the primary outcomes were not related to the modification of one or more pain-related outcome related to acute pain crises. Ultimately three studies, published under the same author, were included in the review: one nonrandomized controlled trial (1998) and two randomized controlled trials (2014 and 2018). The randomized controlled studies (2014 and 2018) have been included in our review and will not be summarized here, however the 1998 nonrandomized controlled trial was not included in our review because it did not report outcomes of interest. The 1998 nonrandomized, single-center 4-week study evaluated the biochemical effects of oral l-glutamine in seven patients aged 18 and older with genotype HbSS. Patients were excluded if they were pregnant, had blood transfusions in the previous 3 months, or would be concurrently receiving hydroxyurea. After 4 weeks, there was a significant increase in NADH levels and NAD redox potential, with all patients (100%) reporting improvements in energy levels and a decrease in chronic pain levels and 6 (86%) reporting improvements in activity levels and decreased narcotics use.

Authors of the systematic review concluded that there is a limited amount of high-quality data to support the use of L-glutamine in patients with SCD and listed several limitations of the evidence supporting its use. Specifically, the studies were all conducted under the same principal

investigator, two trials recruited small sample sizes, and inclusion criteria were not generalizable to the broader SCD population.

Appendix C. Ongoing Studies

Title / Trial Sponsor	Study Design	Study Arms	Patient Population	Primary Outcomes	Estimated Completion Dates
Crizanlizumab					
Pharmacokinetics and Pharmacodynamics Study of SEG101 (Crizanlizumab) in Sickle Cell Disease (SCD) Patients with Vaso-Occlusive Crisis (VOC) **NCT03264989** **Novartis Pharmaceuticals**	Phase II, Multicenter, Open-Label <u>Estimated Enrollment</u>: 57	Intervention: Crizanlizumab 5.0 mg/kg (or 7.5 mg/kg for exploratory group) by IV	<u>Inclusion:</u> 1. Male and non-pregnant female patients 16-70 years of age 2. Confirmed diagnosis of SCD 3. Experienced at least 1 acute pain crisis within the preceding 12 months prior to screening 4. If receiving HU/HC or erythropoietin stimulating agent, must have been receiving the drug for at least 6 months prior to screening <u>Exclusion:</u> 1. History of stem cell transplant 2. Acute pain crisis ending 7 days prior to first dosing 3. Ongoing hospitalization prior to screening 4. Received blood products within 30 days to first dosing 5. Participating in a chronic transfusion program	1. To characterize PK (AUC), PK (Ctrough), PK (Cmax), and PD (AUC for P-selectin inhibition) of crizanlizumab at 5.0 mg.kg	February 2021
Study of Dose Confirmation and Safety of Crizanlizumab in	Phase II, Multicenter, Open-Label	Intervention: Crizanlizumab 5.0 mg/kg	<u>Inclusion:</u> 1. Male or female patients who are 2 to <18 years	1. PK (AUCd15) after 1st dose	August 2022

			2. Confirmed diagnosis of SCD	2. PD (AUCd15) after	
Pediatric Sickle Cell Disease Patients	Estimated Enrollment: 100		3. Experienced at least 1 acute pain crisis within preceding 12 months, as determined by medical history	1st dose 3. PK (AUCtau) after 5th dose	
[NCT03474965](#)			4. If receiving HU/HC or erythropoietin stimulating agent or L-glutamine, must have been	4. PD (AUCtau) after 5th dose	
Novartis Pharmaceuticals			receiving drug for at least 6 months prior to screening and plan to continue taking the same dose and schedule during the trial	5. PK (Cmax) after 1st and 5th dose 6. PK pre-dose concentrations 7. Frequency of any adverse events (AEs) as a measure of safety and tolerability	
			Exclusion: 1. History of stem cell transplant 2.Received any blood products within 30 days of Day 1 dosing 3. Participating in a chronic transfusion program 4. Patients with bleeding disorders		
Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients [NCT03814746](#) **Novartis Pharmaceuticals**	Phase III, Multicenter, Randomized, Double-Blind Estimated Enrollment: 240	Intervention 1: Crizanlizumab 5.0mg/kg Intervention 2: Crizanlizumab 7.5 mg/kg Comparator: Placebo	Inclusion: 1. Male or female aged 12 years and older on day of signing informed consent 2. Confirmed diagnosis of SCD 3. Experienced at least 2 acute pain crises leading to healthcare visit within 12 months prior to screening visit as determined by medical history 4. If receiving HU/HC or erythropoietin stimulating agent or L-glutamine, must have been	1. Rate of acute pain crises events leading to healthcare visit	November 2027

			receiving drug for at least 6 months prior to screening Exclusion: 1.History of stem cell transplant 2. Participation in a chronic transfusion program 3. Contraindication or hypersensitivity to any drug or metabolites from similar class as a study drug or to any excipients of the study drug formulation 4. Received active treatment on another investigational trial within 30 days prior to screening		
A Study to Evaluate the Safety and Efficacy of Crizanlizumab in Sickle Cell Disease Related Priapism **NCT03938454** **Novartis Pharmaceuticals**	Prospective Phase II, Multicenter, Open-Label, Single-Arm Estimated Enrollment: 56	Intervention: Crizanlizumab 5mg/kg IV	Inclusion: 1. Male patients aged 16 years and above 2. Confirmed diagnosis of SCD 3. Experienced 4 or more priapic events over the 14 weeks preceding study participation 4. Experienced at least 3 priapic events during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment Exclusion: 1.Had penile prosthetic implants or shunts or any other surgical procedure on the penis	1. Percent change in priapic events from baseline to 26 weeks	March 2022

			2. Took drugs/medications that may induce priapism over the 14 weeks preceding study entry 3. Received leuprolide acetate (Lupron) within 3 months before pre-screening 4. Had an erection lasting more than 12 hours over the 14 week preceding study entry		
Study Exploring the Effect of Crizanlizumab on Kidney Function in Patients With Chronic Kidney Disease Caused by Sickle Cell Disease NCT04053764 **Novartis Pharmaceuticals**	Phase II, Randomized, Multicenter, Open-Label, Estimated Enrollment: 170	Intervention: Crizanlizumab (5mg/kg) + standard of care Comparator: Standard of care (HU/HC, ACE, and ARBs)	Inclusion: 1. Confirmed diagnosis of SCD 2. Patients with eGFR ≥ 45 ≤ 120 mL/min/1.73 m2 based on CKD EPI formula 3. Patients with ACR of ≥ 100 to ≤ 2000 mg/g 4. Receiving standard of care drugs for SCD and/or CKD for at least 6 months prior to study entry 5. Hb ≥ 4.0 g/dL, absolute neutrophil count (ANC) ≥ 1.0 x 109/L, and platelet count ≥ 75x109/L 6. Written informed consent prior to screening procedures Exclusion: 1. History of stem cell transplant 2. Patients with evidence of AKI within 3 months of study entry 3. Blood pressure > 140/90 mmHg despite treatment	1. Percentage of patients with ≥ 30% decrease in albuminuria (ACR)	July 2022

			4. Patients undergoing hemodialysis 5. Participating in chronic transfusion program 6. History of kidney transplant		
Voxelotor					
Study to Assess the Effect of Long-Term Treatment with GBT440 in Participants Who Have Completed Treatment in Study GBT 440-031 (034 OLE) **NCT03573882** **Global Blood Therapeutics**	Phase III, Open-Label Estimated Enrollment: 179	Intervention: Voxelotor 300mg with or without food	Inclusion: 1. Participants with SCD who participated or received study treatment in study GBT440-031 Exclusion: 1. Participant who was lost to follow-up in previous study 2. Patient requiring chronic dialysis	1. Number of participants with treatment-related adverse events 2. Frequency of sickle-cell complications	December 2024
Dose Escalation Study to Evaluate the Safety, Tolerability, PK, and PD of Voxelotor in Patients with SCD **NCT04247594** **Global Blood Therapeutics**	Phase 2, open-label, multiple dose escalation study Estimated enrollment: 45	Intervention Cohort A: voxelotor administration starting from 1500mg with titration Cohort B: voxelotor doses higher than 1500mg without up-titration	Inclusion: 1. Patients with sickle cell disease (HbSS or $HbSB^0$ 2. Aged 18+ Exclusion: 1. More than 10 VOCs within 10 months of screening 2. Hospitalized for sickle cell crises within past two years requiring chemotherapy and/or radiation 3. History of unstable or deteriorating cardiac or pulmonary disease	1. Treatment-emergent AEs	December 2021

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An Open-Label Extension Study of Voxelotor Administered Orally to Pediatric Participants With Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials **NCT04188509** **Global Blood Therapeutics**	Open-label Extension Estimated Enrollment: 50	Intervention: ≥ 12 years: 1500 mg QD < 12 years: weight-based dose	Inclusion: 1. Participants with SCD, aged ≥ 4 to ≤ 18 2. Participated and received study drug in GBT-sponsored voxelotor pediatric clinical study Exclusion: 1. Participant withdrew consent from GBT-sponsored voxelotor pediatric clinical study	1. Treatment-Emergent Adverse Events 2. Serious Adverse Events 3. Sickle Cell Disease-Related Complications	January 2026
Study to Evaluate the Effect of GBT440 on TCD in Pediatrics With Sickle Cell Disease (HOPE Kids 2) **NCT04218084** **Global Blood Therapeutics**	Phase III Double-Blind, Placebo-Controlled, RCT Estimated Enrollment: 224	Intervention: 1500mg voxelotor or equivalent daily as tablet or powder for oral suspension Comparator matching placebo	Inclusion 1. Participants with SCA 2. Aged ≥ 2 to < 15 years 3. Hb ≥ 5.5 and ≤ 10.5 g/dL 4. TCD time averaged maximum of the mean velocity arterial cerebral blood ≥170 to <200 cm/sec during the screening period Exclusion 1. Body weight <5kg at screening visit 2.Hospitalization for acute pain crisis and ACS within the 14 days prior to execution of informed consent 3. More than 10 acute pain crises within past 12 months requiring hospitalization or clinic visit	1. Transcranial Doppler (TCD)	March 2026

No on-going trials at this time.

Source: www.ClinicalTrials.gov

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to crizanlizumab, voxelotor, and L-glutamine (Endari). These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Tables D1, D7, and D13)[84] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[85]

Figure D1. ICER Evidence Rating Matrix

A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D= "Negative"- High certainty of an inferior net health benefit
B+= "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Any situation in which the level of certainty in the evidence is low

Table D1. Study Quality of Crizanlizumab SUSTAIN Trial[36]

Study	Comparable Groups	Adequate Randomization	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-Up	ITT Analysis	Appropriate Handling of Missing Data	Overall Quality
SUSTAIN Ataga 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

ITT: intent-to-treat

Table D2. Study Design of the SUSTAIN trial[36]

Study	Crizanlizumab (SUSTAIN)
Design	Phase 2, double-blind, randomized, placebo-controlled trial. Patients were randomized 1:1:1 to receive low-dose crizanlizumab (2.5mg/kg of body weight), high dose crizanlizumab (5.0mg/kg of body weight) or placebo and were stratified by number of crises in the preceding year (2 to 4 or 5 to 10) and concomitant hydroxyurea use (yes or no).
Inclusion Criteria	• Sickle cell disease (homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle β^0 thalassemia [HbSβ^0], sickle β^+ thalassemia [HbSβ^+] or other genotypes) • 16-65 years of age • 2 to 10 sickle-cell related pain crises in 12 months before enrollment • Patients on hydroxyurea were required to have been receiving the drug for at least 6-months and were not allowed to have any dose alteration during the 52-weeks. If patients were not on hydroxyurea, it could not be initiated.
Exclusion Criteria	• Patients undergoing long-term red-cell transfusion therapy were excluded
N	198
Interventions	• 2.5mg/kg Crizanlizumab (N=66) • 5.0 mg/kg Crizanlizumab (N=67) • Placebo (N=65)
Follow-up	30-day screening phase, 52-week treatment phase, and a 6-week follow-ep evaluation phase

Study	Crizanlizumab (SUSTAIN)

Outcomes	• *Primary Endpoint:* Annual rate of sickle-cell related pain crises
	• *Secondary Endpoints:*
	   ○ Annual rate of days hospitalized
	   ○ Time to first and second crises
	   ○ Annual rate of uncomplicated crises
	   ○ Annual rate of acute chest syndrome
	   ○ The Brief Pain Inventory Questionnaire

Table D3. Key Baseline Characteristics of the SUSTAIN Trial[36]

Study		Ataga 2017		
Interventions		High-Dose Criz	Low-Dose Criz	Placebo
N		67	66	65
Age, Median (Range)		29 (16-63)	29 (17-57)	26 (16-56)
Female, n (%)		35 (52)	36 (55)	38 (58)
Black, n (%)		60 (90)	62 (94)	60 (92)
Concomitant Hydroxyurea, n (%)	Yes	42 (63)	41 (62)	40 (62)
	No	25 (37)	25 (38)	25 (38)
HbSS Genotype, n (%)	HbSS	47 (70)	47 (71)	47 (72)
	HbSC	9 (13)	15 (23)	8 (12)
	HbSβ0	3 (4)	2 (3)	7 (11)
	HbSβ+	7 (10)	2 (3)	1 (2)
	Other	1 (1)	0 (0)	2 (3)
Sickle-Cell Related Pain crises in past 12 months	2-4	42 (63)	41 (62)	41 (63)
	5-10	25 (37)	25 (38)	24 (37)
Baseline hemoglobin level — g/dl Mean (SD)		9.1 (1.8)	9.2 (1.9)	9.0 (1.5)
No. of vaso-occlusive crises in the past 12 months N(%)		NR	NR	NR

Criz: crizanlizumab, g/dl: grams per deciliter, n: number, NR: not reported, SD: standard deviation

Table D4. Key Efficacy Outcomes in SUSTAIN[10,86,87,89]

Study		Ataga 2017 + Kutlar 2019		
Interventions		High-Dose Criz	Low-Dose Criz	Placebo
N		67	66	65
Acute Pain Crisis	*ITT*			
	Median Rate/year (IQR)	1.63 (0.00-3.97)	2.01 (1.00-3.98)	2.98 (1.25-5.87)
	% Difference; P-Value	-45.3; P=0.01	-32.6; P=0.18	NR; NR
	No. of Patients with crisis rate of zero at end of trial	24	12	11
	PP			
	Median Rate/year (IQR)	1.04 (0.00-3.42)	2.00 (1.00-3.02)	2.18 (1.96-4.96)
	% Difference; P-Value	NR; P=0.01	NR; P-0.13	NR; P=0.02
	No. of Patients with crisis rate of zero at end of trial	15	7	5
Acute Chest Syndrome	Median Rate/year (IQR)	0 (0.00-0.00)	0 (0.00-0.00)	0 (0.00-0.00)
	% Difference; P-Value	0.0; p=0.78	0.0; P=0.87	--
Splenic Sequestration	Median Rate/year (IQR)	NR	NR	NR
	% Difference; P-Value	NR	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)	1.08 (0.00-3.96)	2.00 (0.00-3.02)	2.91 (1.00-5.00)
	% Difference; P-Value	-62.9; P=0.02	-31.3; P=0.12	--
	Acute pain crisis events in the year prior to study			
	Median Rate/year 2-4	1.00 (0-11.8)	NR	1.97 (0-13.3)
	Median Rate/year 5-10	1.85 (0-24.3)	NR	4.84 (0-19.2)
	Genotype			
	Median Rate/year HbSS	1.63 (0-24.3)	NR	3.00 (0-19.2)
	Median Rate/year Non-HbSS	0.99 (0-15.2)	NR	2.00 (0-13.3)
	HU Use			
	Median Rate/year Yes	1.74 (024.3)	NR	3.13 (0-13.5)
	Median Rate/year No	0.98 (0-11.8)	NR	1.98 (0-19.2)
Patients with no acute pain crisis during treatment, n(%)	*ITT*			
	0	24 (35.8)	NR	11 (16.9)
	*PP**			
	0	15 (37.5)	NR	5 (12.2)
	Acute pain crisis events in the year prior to the study			
	2-4	17/42 (40.5)	NR	10/41 (24.4)

Study	Ataga 2017 + Kutlar 2019		
5-10	7/25 (28.0)	NR	1/24 (4.2)
Genotype			
HbSS	15/47 (31.9)	NR	8/47 (17.0)
Non-HbSS	9/20 (45.0)	NR	3/18 (16.7)
HU Use			
Yes	14/42 (33.3)	NR	7/40 (17.5)
No	10/25 (40.0)	NR	4/25 (16.0)
HU use / acute pain crisis events in the year prior to study			
Yes/2-4	11/25 (44.0)	NR	6/24 (25.0)
Yes/5-10	3/17 (17.6)	NR	1/16 (6.3)
No/2-4	6/17 (35.3)	NR	4/17 (23.5)
No/5-10	4/8 (50.0)	NR	0/8 (0.0)
Hepatic Sequestration Median Rate/year (IQR)	NR	NR	NR
% Difference; P-value	NR	NR	NR
Priapism Median Rate/year (IQR)	NR	NR	NR
% Difference; P-value	NR	NR	NR
Hospitalization No Hospitalization	46%	NR	35%
≥1 Hospitalization	54%	NR	65%
Median time to first hospitalization (months)	6.3	NR	3.2
HR [95%CI]	0.683 [0.437-1.066]	NR	0.683 [0.437-1.066]
Median Rate/year (IQR)	4.00 (0.00-25.72)	6.87 (0.00-18.00)	6.87 (0.00-28.30)
% Difference; P-Value	-41.8; P=0.45	0.00; P=0.84	--
Brief Pain Inventory Mean Score Change	Small change*		
Difference; p-value	No significant changes from baseline*		
Time to First Sickle-Cell Related Pain Crisis *ITT*			
Median time (IQR)	4.07 (1.31-NR)	2.20 (0.95-6.60)	1.38 (0.39-4.90)
Hazard ratio (95% CI)	0.50 (0.33-0.74)	0.75 (0.52-1.10)	--
P-Value	0.001	0.14	--
PP			
Median time (IQR)	6.55 (3.02-NR)	NR	1.58 (0.46-4.93)
Hazard ratio (95% CI)	NR	NR	NR
P-Value	0.001	NR	<0.001

Study			Ataga 2017 + Kutlar 2019		
	Acute pain crisis events in the year prior to study				
	2-4	Median time	4.76 (1.81-NR)	NR	1.61 (0.62-6.70)
		Hazard ratio (95% CI)	0.53 (0.31-0.90)	NR	0.53 (0.31-0.90)
	5-10	Median time	2.43 (1.25-7.75)	NR	1.03 (0.30-2.97)
		Hazard ratio (95% CI)	0.47 (0.25-0.89)	NR	0.47 (0.25-0.89)
	Genotype				
	HbSS	Median time	4.07 (1.31-NR)	NR	1.12 (0.33-4.17)
		Hazard ratio (95% CI)	0.50 (0.31-0.80)	NR	0.50 (0.31-0.80)
	Non-HbSS	Median time	6.90 (1.41-NR)	NR	3.09 (1.12-6.21)
		Hazard ratio (95% CI)	NR	NR	0.47 (0.21-1.05)
	HU Use				
	Yes	Median time	2.43 (1.15-NR)	NR	1.15 (0.33-4.90)
		Hazard ratio (95% CI)	0.58 (0.35-0.96)	NR	0.58 (0.35-0.96)
	No	Median time	5.68 (3.09-NR)	NR	2.86 (0.79-4.53)
		Hazard ratio (95% CI)	0.39 (0.20-0.76)	NR	0.39 (0.20-0.76)
Time to Second Sickle-Cell Related Pain Crisis	*ITT*				
	Median time (IQR)		10.32 (4.47-NR)	9.20 (3.94-12.16)	5.09 (2.96-11.01)
	Hazard ratio (95% CI)		0.53 (0.33-0.87)	0.69 (0.44-1.09)	--
	P-Value		0.02	0.1	--
	HU Use: No				
	Hazard ratio (95% CI)		0.40 (0.17-0.93)	NR	0.40 (0.17-0.93)
	Non-HbSS Genotype				
	Hazard ratio (95% CI)		0.30 (0.11-0.81)	NR	0.30 (0.11-0.81)

CI: confidence interval, Criz: crizanlizumab, HU: hydroxyurea, IQR: interquartile range, ITT: intent-to-treat, NR: not reported, PP: per-protocol

*language taken directly from trial

**abstract only reports on patients with no acute pain crises during treatment

Table D5. Key Safety Events in SUSTAIN[10,89]

Study		Ataga 2017 + Kutlar 2019		
Interventions		High-Dose Criz	Low-Dose Criz	Placebo
N		66	64	62
No. of patients with ≥1 Serious Adverse Events, n (%)		17 (26)	21 (33)	17 (27)
Treatment – Emergent Adverse Events, Number of events; n (%)	2-4 acute pain crises	313; 36 (87.8)	NR	217; 34 (87.2)
	5-10 acute pain crises	146; 21 (84.0)	NR	141; 21 (91.3)
	HbSS Genotype	312; 39 (84.8)	NR	255; 38 (86.4)
	Non-HbSS Genotype	147; 18 (90.0)	NR	103; 17 (94.4)
	HU Use: Yes	242; 35 (85.4)	NR	226; 35 (89.7)
	HU Use: No	217; 22 (88.0)	NR	132; 20 (87.0)
Adverse Events Leading to Discontinuation, Number of events; n (%)	2-4 acute pain crises	1; 1 (2.4)	NR	1; 1 (2.6)
	5-10 acute pain crises	1; 1 (4.0)	NR	6; 2 (8.7)
	HbSS Genotype	1; 1 (2.2)	NR	6; 2 (4.5)
	Non-HbSS Genotype	1; 1 (5.0)	NR	1; 1 (5.6)
	HU Use: Yes	0; 0 (0.0)	NR	7; 3 (7.7)
	HU Use: No	2; 2 (8.0)	NR	0; 0 (0.0)
Most Frequent Adverse Events, n (%)				
Pyrexia		2 (3)	0	1 (2)
Influenza		0	3 (5)	0
Pneumonia		3 (5)	2 (3)	3 (5)
Adverse Events, n (%)				
Headaches		11 (17)	14 (22)	10 (16)
Back Pain		10 (15)	13 (20)	7 (11)
Urinary Tract Infection		9 (14)	7 (11)	7 (11)
Nausea		12 (18)	11 (17)	7 (11)
Arthralgia		12 (18)	9 (14)	5 (8)
Pain in Extremity		11 (17)	8 (12)	10 (16)
Upper respiratory tract infection		7 (11)	7 (11)	6 (10)
Pyrexia		7 (11)	6 (9)	4 (6)

Study	Ataga 2017 + Kutlar 2019		
Diarrhea	7 (11)	5 (8)	2 (3)
Musculoskeletal Pain	8 (12)	4 (6)	6 (10)
Pruritus	5 (8)	7 (11)	3 (5)
Vomiting	5 (8)	7 (11)	3 (5)
Chest Pain	1 (2)	7 (11)	1 (2)

Criz: crizanlizumab, HU: hydroxyurea, N: number

D6. Study Quality of Voxelotor HOPE Trial

Study	Comparable Groups	Adequate Randomization	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-Up	ITT Analysis	Appropriate Handling of Missing Data	Overall Quality
HOPE Vichinsky 2019	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Good

ITT: intent-to-treat

Table D7. Study Design of Voxelotor Trials[37]

Study	Voxelotor (HOPE)
Design	Phase 3, double-blind, randomized, multi-center, placebo-controlled trial. Patients were randomized 1:1:1 to receive a once-daily high-dose (1500 mg) oral dose of voxelotor, low-dose (900 mg) of voxelotor, or placebo. Stratification factors included hydroxyurea use (yes or no), geographic region (North America, Europe, or other), and age (adolescent [12-17 years] or adults [18 to 65 years]).
Inclusion Criteria	• Ages 12-65 with confirmed sickle cell disease (homozygous hemoglobin S, sickle hemoglobin C disease, hemoglobin Sβ-thalassemia, or other genotypic variants of SCD) • Hemoglobin level between 5.5 and 10.5 g/dl • 1-10 vaso-occlusive crises in past 12 months • Participants receiving hydroxyurea at a stable dose (at least 3 months) were eligible
Exclusion Criteria	• Participants receiving regular red-cell transfusion therapy, had received transfusion in past 60 days, or had been hospitalized for vaso-occlusive crisis within 14 days before providing informed consent
N	274
Interventions	• Voxelotor 1500 mg (n=90) • Voxelotor 900 mg (n=92) • Placebo (n=92)
Follow-up	28-35 day Screening Period, up to 72 week Treatment Period and End-of-trial visit at 4 weeks after last dose.

Study	Voxelotor (HOPE)

Outcomes	• *Primary Endpoint:* % participants with hemoglobin response
	• *Secondary Endpoints:*
	    ○ Change in hemoglobin from BL to wk 24
	    ○ Lab markers associated with hemolysis (indirect bilirubin level, absolute reticulocyte count, % reticulocytes, lactate dehydrogenase level)
	    ○ Annualized incidence rate of vaso-occlusive crisis

Table D8. Key Baseline Characteristics of Voxelotor trials[37]

Study		Vichinsky 2019	
Interventions		High-Dose VOX	Placebo
N		90	92
Age, Median (Range)		24	28
Female, n (%)		58 (64)	50 (54)
		59 (66)	63 (68)
Concomitant Hydroxyurea, n (%)	Yes	58 (64)	58 (63)
	No	32 (36)	34 (37)
HbSS Genotype, n (%)	HbSS	61 (68)	74 (80)
	HbSC	3 (3)	2 (2)
	HbSβ0	18 (20)	11 (12)
	HbSβ+	7 (8)	3 (3)
	Other	1 (1)	2 (2)
Baseline hemoglobin level — g/dl Median (range)		8.7 (5.9-10.8)	8.6 (6.1-10.5)
No. of vaso-occlusive crises in the past 12 months N(%)	0	NR	NR
	1	35 (39)	39 (42)
	2-10	55 (61)	53 (58)
Hospitalizations due to painful crisis in the past 12 months, Median (range)		NR	NR

VOX: voxelotor, N: number, %: percent, g/dL: grams per deciliter

Table D9. Key Efficacy Outcomes in Voxelotor trials[11,37]

Study		Vichinsky 2019	
Interventions		High-Dose VOX	Placebo
N		90	92
Acute Pain Crisis	Median Rate per-person-year (95%CI)	2.77 (2.15-3.57)	3.19 (2.50-4.07)
	% Difference P-Value	NR	NR
	No. of Patients with crisis rate of zero at end of trial	≥1: 59(67)	≥1: 63 (69)
28-day Observation Period for Patients who Discontinued VOX			
N		21	17
Acute pain crises reported		6	8
Number of patients reporting acute pain crises		5	5
Incidence Rate		4.63	7.01
Secondary and Tertiary Outcomes			
Acute Chest Syndrome	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Splenic Sequestration	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Painful Sickle Cell Crisis (PSCC) %	0	NR	NR
	1	NR	NR
	2	NR	NR
	3	NR	NR
Hepatic Sequestration	Median Rate/year (IQR)	NR	NR
	% Difference; P-value	NR	NR
Priapism	Median Rate/year (IQR)	NR	NR
	% Difference; P-value	NR	NR
Hospitalization	Median Rate/year (IQR)	NR	NR
	% Difference ;P-Value	NR	NR
Brief Pain Inventory	Mean Score Change	NR	NR

Study		Vichinsky 2019	
	Difference ; p-value	NR	NR
Time to First Sickle-Cell Related Pain Crisis	Median time (IQR)	NR	NR
	Hazard ratio (95% CI)	NR	NR
	P-Value	NR	NR
Time to Second Sickle-Cell Related Pain Crisis	Median time (IQR)	NR	NR
	Hazard ratio (95% CI)	NR	NR
	P-Value	NR	NR
Hemoglobin Response, n (%)		46 (51)	6 (7)
Absolute change in Hemoglobin (g/dL)	No. of participants	88	91
	LS Mean (95% CI)	1.1 (0.9-1.4)	-0.1 (-0.3-0.2)
Indirect Bilirubin	No. of participants	85	85
	LS Mean (95% CI)	-29.1 (-35.9 to -22.2)	-3.2 (-10.1 to 3.8)
Percentage of Reticulocytes	No. of participants	88	91
	LS Mean (95% CI)	-19.9 (-29.9 to - 10.9)	4.5 (-4.5 to 13.6)
Absolute Reticulocyte Count	No. of participants	88	91
	LS Mean (95% CI)	-8.0 (-18.1 to2.1)	3.1 (-7.0 to 13.2)
Lactate Dehydrogenase	No. of participants	88	97
	LS Mean (95% CI)	-4.5 (-11.9 to 2.8)	3.4 (-4.0 to 10.9)

IQR: interquartile range, CI: confidence interval, LS: least squares, VOX: voxelotor

Table D10. Subgroup Analyses of HOPE Trial[146,147]

Study		Vichinsky 2019	
		High Dose VOX	Placebo
Mean Percent Change in Hemolysis Markers by change in Hb at 24 weeks - PP			
N		**74**	**76**
Absolute Reticulocyte	Change in Hb >1g/ dL	-16.7	NR
	Change in Hb ≤1 g/ dL	1.5	NR
Percent of Reticulocytes	Change in Hb >1g/ dL	-35.2	NR
	Change in Hb ≤1 g/ dL	-3.6	NR
Indirect Bilirubin	Change in Hb >1g/ dL	-37.0	NR
	Change in Hb ≤1 g/ dL	-24.9	NR
LDH	Change in Hb >1g/ dL	-11.0	NR
	Change in Hb ≤1 g/ dL	-1.1	NR
Mean Change (95% CI) in laboratory parameters from Baseline to Week 24			
Hb g/dL	Hydroxyurea Use - Yes	1.3 (1.0, 1.6)	0.0 (-0.2 , 0.2)
(N=229)	Hydroxyurea Use - No	1.3 (0.8, 1.8)	0.0 (-0.2, 0.3)
HbF %	Hydroxyurea Use - Yes	-1.8 (-3.1, -0.5)	-0.1 (-1.8, 1.5)
(n=131)	Hydroxyurea Use - No	0.2 (-0.9, 1.3)	0.5 (0.0, 1.1)

Hb: hemoglobin, HbF: fetal hemoglobin, g/dL: grams per deciliter, VOX: voxelotor, PP: per protocol, LDH: lactate dehydrogenase

Table D11. Key Safety Events in Voxelotor trials[11,146]

Study	Vichinsky 2019		Howard 2019
Interventions	High-Dose VOX	Placebo	VOX 900mg
N	90	92	7
Serious Adverse Events, n (%)	17 (19.3)	15 (16.5)	0 (0)
Treatment -Emergent Adverse Events, n (%)	83 (94.3)	81 (89.0)	0 (0)
Adverse Events Leading to Discontinuation, n (%)	8 (9.1)	4 (4.4)	0 (0)
Headaches, n(%)	23 (26)	20 (22)	2 (29)
Back Pain, N(%)	10 (11)	10 (11)	2 (29)
Urinary Tract Infection, N(%)	NR	NR	NR
Nausea, n(%)	15 (17)	9 (10)	NR
Deaths, n (%)	NR	NR	0 (0)

VOX: voxelotor, N: number

Table D12. Study Quality of L-Glutamine[9,90]

Study	Comparable Groups	Adequate Randomization	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-Up	ITT Analysis	Appropriate Handling of Missing Data	Overall Quality
Niihara 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Niihara 2014	No	No	Yes	Yes	N/A	No	Yes	No	Poor

ITT: intent-to-treat

Table D13. Study Design of the L-Glutamine Trials[9,90]

Study	L-Glutamine (Endari)	Niihara 2014
Design	Phase III, year-long, randomized, placebo-controlled, double-blind, parallel-group trial. Participants were randomized 2:1 to receive L-glutamine or placebo with randomization stratified by region of participating site and status with respect to hydroxyurea use.	Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Participants were randomized 1:1 to oral L-glutamine at 0.3 grams per kilogram or oral placebo twice daily for 48 weeks
Inclusion Criteria	• Sickle cell anemia (homozygous hemoglobin S [HbSS]), or sickle cell thalassemia (HbSβ[0]-thalassemia) • At least 5 years of age • Had at least 2 pain crises (no upper limit) documented in the previous year Patients who were receiving treatment with hydroxyurea at a dose that had been stable or at least 3 months before screening and who intended to continue that treatment were eligible to participate.	• Sickle cell anemia or sickle β0-thalassemia as documented by hemoglobin electrophoresis • At least 5 years old • At least 2 episodes of painful crises within 12 months of the screening visit
Exclusion Criteria	• Hospitalized for a reason not related to sickle cell disease within 2 months before screening • Prothrombin-time international normalized ration higher than 2.0 • Serum albumin level ration higher than 3.0g • Clinically significant renal or liver disease • Had treatment with L-glutamine within 30 days before screening.	• Significant medical condition that required hospitalization within 2 months of the screening visit • Diabetes mellitus • Treated with an experimental drug within 30 days of screening visit
N	230	62
Interventions	• L-Glutamine (N=152) • Placebo (N=78)	• L-Glutamine (N=33) • Placebo (N=29)
Follow-up	48-week treatment period followed by a 3-week tapering period and an observation period of 2 weeks. Total trial duration of 53 weeks.	48-week treatment period with a 3-week tapering period. Final visit 2 weeks post final dose of study at week 53.

Outcomes	• *Primary Endpoint:* Number of pain crises through week 48
	• *Secondary Endpoints:*
	  o Number of hospitalizations for SC-related pain
	  o Number of ED visits
	  o Changes in hemoglobin measures
		• *Primary Endpoint:* frequency of painful sickle cell crises
		• *Secondary Endpoints:* frequency of hospitalizatios for sickle cell pain, frequency of emergency room visits for sickle cell pain, number of days patients' usual daily activities were interrupted due to sickle cell pain, heigh and weight.

Table D14. Key Baseline Characteristics of L-Glutamine Trials[9,90,91,149]

Study		Niihara 2018 NEMJ + Blood + 2015		Niihara 2014	
Interventions		L-Glutamine	Placebo	L-Glutamine	Placebo
N		152	78	33	29
Age, Median (Range)		19 (5 to 57)	17 (5 to 58)	29.0 (13-58)	26.0 (9-55)
Age Group (Years)	5-12	34 (22.4)	17 (21.8)	0.00	2 (6.9)
	13-18	41 (27)	26 (33.3)	3 (9.1)	1 (3.4)
	>18	77 (50.7)	35 (44.9)	20 (91)	26 (89.6)
Female, n (%)		79 (52)	45 (57.7)	22 (66.7)	10 (34.5)
Black, n (%)		144 (94.7)	73 (93.6)	32 (97.0)	28 (6.6)
Concomitant Hydroxyurea, n (%)	Yes	101 (66.4)	52 (66.7)	NR	NR
	No	NR	NR	NR	NR
HbSS Genotype, n (%)	HbSS	136 (89.5)	71 (91.0)	31 (93.9)	24 (82.8)
	HbSC	NR	NR	NR	NR
	HbSβ⁰	14 (9.2)	7 (9.0)	2 (6.1)	5 (17.2)
	HbSβ⁺	2 (1.3)	0 (0)		
	Other	NR	NR	NR	NR
Sickle-Cell Related Pain crises in past 12 months, no. (%)	0-1	1 (0.7)	1 (1.3)	NR	NR
	2-5	128 (84.2)	61 (78.2)	NR	NR
	6-9	15 (9.9)	14 (17.9)	NR	NR
	≥ 10	8 (5.3)	2 (2.6)	NR	NR

Study	Niihara 2018 NEMJ + Blood + 2015		Niihara 2014	
Baseline hemoglobin level — g/dl Median (range)	8.8 ± 1.4	8.7 ± 1.2	NR	NR
Hematocrit level at baseline – g/dl	27.7 ± 4.4	27.5 ± 3.6	NR	NR
No. of vaso-occlusive crises in the past 12 months N(%)	NR	NR	NR	NR

NR: not reported, g/dl: grams per deciliter, n: number

Table D15. Key Efficacy Outcomes in L-Glutamine Trials[9,90,91,149]

Study		Niihara 2018 NEJM + Niihara 2018 Blood + Niihara 2015		Niihara 2014	
Interventions		L-Glutamine	Placebo	L-GLutamine	Placebo
N		152	78	33	29
Acute Pain Crisis	Median (range)	3 (0-15)	4 (0-15)	NR	NR
	% Difference P-Value	NR; P=0.005		NR	NR
Acute Chest Syndrome	No. of episodes n(%)				
	0	139 (91.4)	60 (76.9)	NR	NR
	≥ 1	13 (8.6)	18 (23.1)	NR	NR
	1	10 (6.6)	13 (16.7)	NR	NR
	2	3 (2.0)	4 (5.1)	NR	NR
	3	0 (0)	1 (1.3)	NR	NR
	% Difference; P-Value	NR; P=0.003		NR	NR
Splenic Sequestration	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-Value	NR	NR	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-Value	NR	NR	NR	NR
Painful Sickle Cell Crisis (PSCC)	0	24%	10%	NR	NR
	1	6%	8%	NR	NR
	2	36	35%	NR	NR
	3	34%	47%	NR	NR
	Week 24				
	Mean number of Events (SD)	NR	NR	2.5 (2.55)	5.5 (8.46)
	P-Value	NR		0.060	
	Week 48				
	Mean number of events (SD)	NR	NR	4.5 (5.37)	10.8 (18.74)
	P-Value	NR		0.076	
Hepatic Sequestration	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-value	NR	NR	NR	NR

Study		Niihara 2018 NEJM + Niihara 2018 Blood + Niihara 2015		Niihara 2014	
Priapism	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-value	NR	NR	NR	NR
No. of hospitalization for sickle cell-related pain	Median (range)	2 (0-14)	3 (0-13)	NR	NR
	% Difference ;P-Value	NR; P=0.005		NR	
	Week 24				
	Mean	NR	NR	0.8	1.3
	P-Value	NR		0.036	
	Week 48				
	Mean	NR	NR	1.5	2.3
	P-Value	NR		0.072	
No. of Emergency department visits for sickle cell related pain	Median (range)	1 (0-12)	1 (0-15)	NR	NR
	P-Value	0.09		NR	
	Week 24				
	Mean	NR	NR	3.7	9.4
	P-Value	NR		0.105	
	Week 48				
	Mean	NR	NR	1.9	4.7
	P-Value	NR		0.129	
Cumulative no. of days in hospital	Median (range)	6.5 (0-94)	11 (0-187)	NR	NR
	P-Value	0.02		NR	NR
Brief Pain Inventory	Mean Score Change	NR	NR	NR	NR
	Difference; p-value	NR	NR	NR	NR
Time to First Sickle-Cell Related Pain Crisis	Median time (IQR)	84 (NR)	54 (NR)	NR	NR
	Hazard ratio (95% CI)	0.69 (0.52-0.93)		NR	NR
	P-Value	0.02		NR	NR
Time to Second Sickle-Cell Related Pain Crisis	Median time (IQR)	212 (NR)	133 (NR)	NR	NR
	Hazard ratio (95% CI)	0.68 (0.49-0.96)		NR	NR
	P-Value	0.03		NR	NR
Mean Corpuscular Volume (MCV)					
Not receiving hydroxyurea	Mean (SD)	94.9 (10.2)		NR	NR
Receiving Hydroxyurea	Mean (SD)	104.0 (13.9)		NR	NR
NADH (mmol/ml RBC)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Total NAD (mmol/ml RBC)	Mean ± SD (range)	NR	NR	NR	NR

Study		Niihara 2018 NEJM + Niihara 2018 Blood + Niihara 2015		Niihara 2014	
	P-value	NR	NR	NR	NR
Redox Potential (%)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Hemoglobin (g/dL)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Subjective Clinical Response					
Energy Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR
Activity Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR
Chronic Pain Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR
Narcotics Dosage	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR

IQR: interquartile range, CI: confidence interval, SD: standard deviation, NR: not reported, n: number, n/s: not significant

Table D16. Key Safety Events in L-Glutamine Trials[9,909,909,90]

Study	Niihara 2018		Niihara 2014	
Interventions	L-Glutamine	Placebo	L-Glutamine	Placebo
N	152	78	37	33
Adverse Events (%)	98%	100%	94.6%	90.9%
Serious Adverse Events, n (%)	78.2%	87.1%	64.7%	63.6%
Sickle Cell Crisis (%)	NR	NR	59.5%	51.5%
Treatment - Emergent Adverse Events, n (%)	NR	NR	NR (8.1%)	NR (9.1%)
Adverse Events Leading to Discontinuation, n (%)	NR	NR	19 (51.4%)	21 (63.6%)
Cardiac Disorders				
Tachycardia	8 (5.3)	4 (5.1)	NR	NR
Gastrointestinal Disorders				
Constipation	38 (25.2)	19 (24.4)	NR	NR
Nausea	34 (22.5)	13 (16.7)	NR	NR
Vomiting	22 (14.6)	10 (12.8)	NR	NR
Abdominal pain upper	16 (10.6)	6 (7.7)	NR	NR
Diarrhea	12 (7.9)	5 (6.4)	NR	NR
Gastroenteritis	NR	NR	5%	15%
General Disorders and administration site conditions				
Chest Pain (noncardiac)	21 (13.9)	7 (9.0)	NR	NR
Fatigue	9 (6.0)	1 (1.3)	NR	NR
Infections and Infestations				
Urinary Tract Infection	10 (6.6)	3 (3.8)	NR	NR
Musculoskeletal and connective tissue disorders				
Pain in Extremity	24 (15.9)	6 (7.7)	NR	NR
Back Pain	20 (13.2)	5 (6.4)	NR	NR
Arthralgia	NR	NR	5%	21%

Study	Niihara 2018		Niihara 2014	
Nervous System Disorders				
Headache	32 (21.2)	14 (17.9)	NR	NR
Dizziness	8 (5.3)	4 (5.1)	NR	NR
Respiratory, Thoracic, and Mediastinal disorders				
Nasal Congestion	11 (7.3)	5 (6.4)	NR	NR

NR: not reported.

Niihara 1998 saw no adverse reactions.

Table D17. Unpublished L-Glutamine Studies

Unpublished L-Glutamine Studies[38]						
Title / Trial Sponsor	**Study Design**	**Study Arms**	**Patient Population**	**Primary Outcomes**	**Results**	**Completion Dates**
L-Glutamine Therapy for Sickle Cell Anemia NCT00586209 **Sponsor: Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center Collaborator: Emmaus Medical Inc.**	Prospective Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Assignment Enrollment: 15 4-week screening period 12-week treatment period 5 week tapering period	Intervention: Weight-based L-Glutamine with upper limit of daily dose at 30g/day (n=5) Comparator: Placebo (n=10)	Inclusion: 1. Subjects (≥18 years of age) with sickle cell anemia or sickle β0-thalassemia. 2. At least two episodes of painful crises within 12 months of screening Exclusion: 1. Significant medical condition requiring hospitalization within 2 months of screening 2. Diabetes mellitus with untreated fasting blood sugar >115 mg/dL	1. Number of occurrences of painful sickle cell crises	**Adverse Events n (%)** L-Glutamine: 4 (80) Placebo: 7 (70) **Serious Adverse Events n (%)** L-Glutamine: 2 (40) Placebo: 5 (50) **Diarrhea** L-Glutamine: 2 (40) Placebo: NR **Nausea / Vomiting** L-Glutamine: 2 (40) Placebo: NR **Sickle Cell Crisis** L-Glutamine: 1 (20) Placebo: NR **Hypertension** L-Glutamine: 1 (20) Placebo: NR	November 2009 **Note from manufacturer:** This study was not published because it did not reach the targeted enrollment of 50 subjects and the decision was made to terminate the study.
Legacy Study 8775	Phase 2a, Randomized, Single-Center, Double-Blind,	Intervention: Oral L-Glutamine 30g/day (10 g, TID)	Inclusion: 1. Subjects (≥18 years of age) with a diagnosis of sickle cell anemia	1. Total NAD 2. NAD redox potential 3. RBC endothelial cell adhesiveness	Of the 6 evaluable patients, there was a significant increase in number of painless days (p=0.00885).	Unknown **Note from manufacturer:** Since

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| | Placebo-Controlled Crossover

Enrollment: 24

24-week treatment period followed by 5 week tapering period prior to crossover | Comparator:
Placebo | 2. At least 3 episodes of painful crises during the 12 month period prior to randomization

Exclusion:
None Reported | 4. Hematologic parameters
5. Frequency of painful crises
6. Number of hospitalization day
7. Number of painless days
8. Safety. | The improvement in number of painful crises was not statistically significant (p=0.28). | only 6 out of 24 patients completed the trial, there was insufficient data for primary endpoint analysis. |
| NAD: nicotinamide adenine dinucleotide, NR: not reported, RBC: red blood cell, TID: three times a day | | | | | | |

Outcomes of Interest

Clinical Outcomes	
Acute	**Chronic**
Acute Pain Episode	Chronic Pain
Stroke/Cerebrovascular Accident	Fatigue
Retinal Infarct	Anxiety
Septicemia	Depression
Acute Chest Syndrome	Neurocognitive Dysfunction
Pneumonia	Retinopathy
Splenic Sequestration	Opioid Dependence/Tolerance
Splenic Infarct	Cardiomyopathy
Sickle Cell Nephropathy	Diastolic Heart Failure
Acute Kidney Injury	Pulmonary Hypertension
Pregnancy Complications	Anemia
Priapism	Erectile Dysfunction
Gallstones	Chronic Kidney Disease
Osteomyelitis	Skin Ulcer
Bone Marrow Infarction	Avascular Necrosis
	Hearing Loss

Biomarkers/Surrogate Endpoints
Hemoglobin (Hb) Level
Fetal Hb Level
Hematocrit
Oxygen percent saturation

Mortality
Cause-specific mortality
All-cause mortality
Survival

Functional Outcomes/Health Related Quality of Life
Cognitive Function
Physical Function
Health-related quality of life
Missed days at school/work
Ability to return to usual activities
Patient satisfaction with treatment

Health Resource Utilization
Emergency department visits
Acute/ urgent care visits
Hospitalization
ICU Admission
Length of hospital stay
Need for blood transfusion

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	**Societal**	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	X	

NA: not applicable, Other impacts: caregiver utility
Adapted from Sanders et al.[148]

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[149]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E2. Age-specific Annual Probability of Death

Age	Percent that die at each age	Probability of Death	Probability of Death (Annual)	Adjusted by Risk Factors
<1	1.5%	0.0150	0.0150	0.0013
1-4	2%	0.0203	0.0051	0.0004
5-9	1.5%	0.0155	0.0031	0.0003
10-14	1.5%	0.0158	0.0032	0.0003
15-19	4%	0.0428	0.0087	0.0007

Age	Percent that die at each age	Probability of Death	Probability of Death (Annual)	Adjusted by Risk Factors
20-24	8%	0.0894	0.0186	0.0016
25-34	20%	0.2454	0.0278	0.0023
35-44	27%	0.4390	0.0562	0.0047
45-54	20%	0.5797	0.0830	0.0070
55-64	11%	0.7586	0.1325	0.0111
65-74	2%	0.5714	0.0812	0.0068
75-84	1.5%	1.0000	0.9688	0.0812

Table E3. Undiscounted Results for the Base Case for Crizanlizumab versus Optimal Usual Care Alone: Health Care Perspective

Treatment	Usual Care	Crizanlizumab	Difference	Incremental cost-effectiveness ratio	
Treatment Cost	-	$1,382,011	$1,382,011	-	
Other Cost	$1,634,306	$1,566,653	-$67,653	-	
Total Cost	$1,634,306	$2,948,663	$1,314,358	-	
VOC	58.37	38.49	19.89	$66,087	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	19.46	23.45	4.00	$328,966	per LY gained
evLYG	10.93	14.07	3.14	$419,114	per evLY gained
QALYs	10.93	12.44	1.51	$868,509	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table E4. Undiscounted Results for the Base Case for Voxelotor versus Usual Care Alone: Health Care Perspective

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio	
Treatment Cost	-	$1,599,084	$1,599,084	-	
Other Cost	$1,634,306	$1,717,584	$83,278	-	
Total Cost	$1,634,306	$3,316,668	$1,682,362	-	
VOC	58.37	59.78	-1.40	$1,197,555	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$56,529	per g/dL year
LYs	19.46	23.57	4.12	$271,436	per LY gained
evLYG	10.93	14.46	3.53	$316,708	per evLY gained
QALYs	10.93	12.91	1.98	$563,336	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Table E5. Undiscounted Results for the Base Case for L-glutamine versus Optimal Usual Care Alone: Health Care Perspective

Treatment	Usual Care	L-Glutamine	Difference	Incremental cost-effectiveness ratio	
Treatment Cost	-	$414,736	$414,736	-	
Other Cost	$1,634,306	$1,587,250	-$47,056	-	
Total Cost	$1,634,306	$2,001,985	$367,680	-	
VOC	58.37	46.85	-11.52	$31,905	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	19.46	21.39	1.93	$124,103	per LY gained
evLYG	10.93	12.40	1.47	$163,805	per evLY gained
QALYs	10.93	11.66	0.73	$329,264	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year

Description of Competing Events Calculations

To simplify the model, it was assumed that only one chronic condition and one acute condition could occur each cycle. This creates a situation where chronic conditions and acute conditions become competing events. Therefore, by decreasing one event in the model it allows other events to occur more frequently. To correct for the competing events, the model was calibrated to minimize the

difference in the number of acute events and chronic conditions because of the reduction in acute pain crises in the treatment arm. Specifically, the steps were to:

1. Remove the risks of acute pain crisis from the model, i.e., make all risk factors of acute pain crisis equal to 1

2. Run the model with the treatment effect as reported in the appropriate trial

3. Calculate adjustment factors that minimize the difference in each acute and chronic condition other than acute pain crisis, since treatment effects should only affect acute pain crisis without the risk factors applied; there was a small effect due to competing events

4. Add the risks of acute pain crisis on the other acute and chronic conditions back into the model

5. Calculate results of the model.

This method can be validated by investigating how the model predicts acute and chronic conditions compared to known SCD populations, as was done in the validation section above.

One-Way Sensitivity Analyses

Table E.6. Sensitivity Analysis of Crizanlizumab Compared to Usual Care: Modified Societal Perspective

Analysis	Incremental Cost-Effectiveness Ratios		
	LYG	evLYG	QALYs
Base case	$345,901	$407,603	$815,865
Double baseline risks	$216,005	$252,367	$522,723
Half baseline risks	$520,529	$605,828	$1,180,197
Double baseline death risk	$340,143	$410,268	$779,088
Half baseline death risk	$355,999	$404,605	$862,038
Baseline HRQoL +20%	$345,901	$403,716	$676,044
Baseline HRQoL -20%	$345,901	$410,160	$1,021,795
Health State Costs +20%	$335,660	$395,535	$791,710
Health State Costs -20%	$356,147	$419,677	$840,031

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life year gained, QALY: quality-adjusted life year

Table E.7. Sensitivity Analysis of Voxelotor Compared to Usual Care: Modified Societal Perspective

Analysis	Incremental Cost-Effectiveness Ratios		
	LYG	evLYG	QALYs
Base case	$472,248	$506,280	$862,542
Double baseline risks	$380,190	$411,485	$732,535
Half baseline risks	$598,270	$633,905	$1,056,463
Double baseline death risk	$447,323	$496,599	$829,608
Half baseline death risk	$516,991	$527,832	$921,377
Baseline HRQoL +20%	$472,248	$495,991	$726,957
Baseline HRQoL -20%	$472,248	$516,441	$1,060,008
Health State Costs +20%	$471,979	$505,992	$862,050
Health State Costs -20%	$472,517	$506,569	$863,034

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life year gained, QALY: quality-adjusted life year

Table E.8. Sensitivity Analysis of L-Glutamine Compared to Usual Care: Modified Societal Perspective

Analysis	Incremental Cost-Effectiveness Ratios		
	LYG	evLYG	QALYs
Base case	$41,530	$47,048	$98,829
Double baseline risks	Dominates	Dominates	Dominates
Half baseline risks	$108,281	$118,118	$249,167
Double baseline death risk	$38,889	$44,825	$89,188
Half baseline death risk	$43,863	$48,094	$108,026

Analysis	Incremental Cost-Effectiveness Ratios		
	LYG	evLYG	QALYs
Baseline HRQoL +20%	$41,530	$46,196	$81,651
Baseline HRQoL -20%	$41,530	$47,749	$124,185
Health State Costs +20%	$29,367	$33,269	$69,884
Health State Costs -20%	$53,698	$60,833	$127,786

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life year gained, QALY: quality-adjusted life year

Probabilistic Sensitivity Analysis

Uncertainty was incorporated into the model estimations using probabilistic sensitivity analysis. To determine the number of simulations needed to estimate a stable estimate, we estimated the cost per QALY with 1 through 1000 simulations to determine at what point additional simulations would not affect the estimate. Analyses for all three comparisons were stable at 1000 simulations.

Figure E1: The Number of Simulations Necessary for Stability
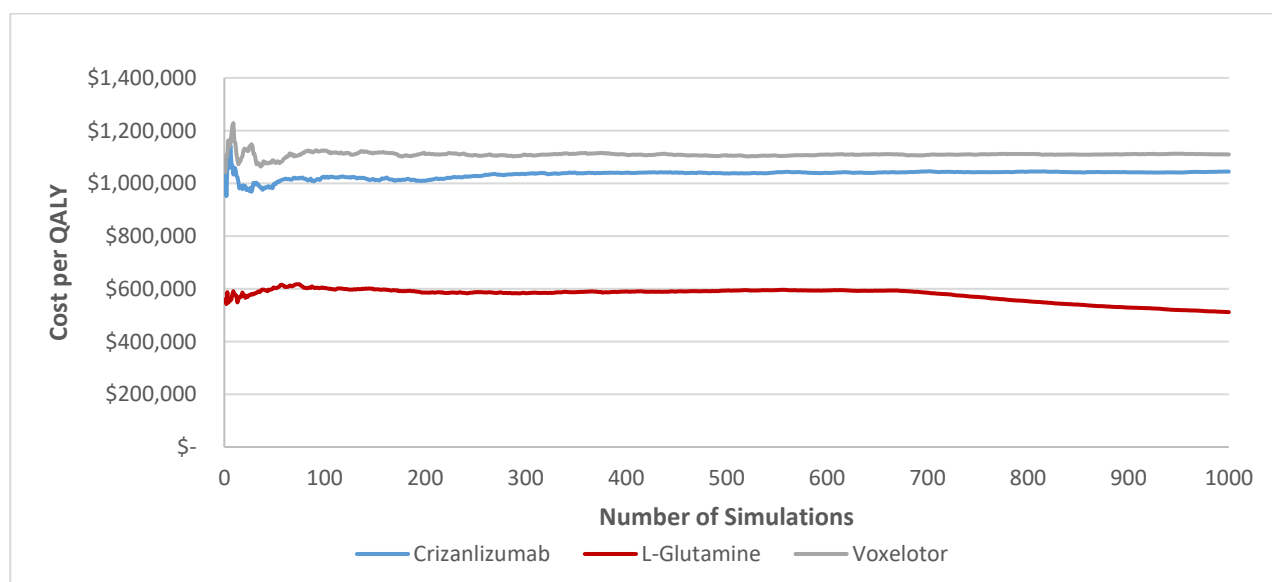
These tables report the average for each output across the 1000 simulations and the 95% credible interval (i.e., the 2.5th and 97.5th percentiles). The probabilistic outputs are very similar to the

deterministic outputs. The credible intervals demonstrate some large variations in the total costs, pain crises, life-years gained, evLYG and QALYs from the parameter uncertainty.

Table E9: Probabilistic Results for Crizanlizumab Compared to Usual Care

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio (Probability cost-effective at $1 million per QALY)	
Total Cost	$1,587,754	$2,780,763	$1,193,010	-	
(95% CI)	($1,325,103,$1,929,148)	($2,438,672,$3,141,650)	($1,075,386,$1,253,816)		
VOC	51.75	34.39	-17.37	$68,695	per VOC avoided
(95% CI)	(46.72,58.43)	(15.10,50.28)	(-37.40,-2.23)		
Hemoglobin (g/dL)	-0.10	1.10	1.20	$48,295	per g/dL
(95% CI)	(-0.31,0.10)	(0.91,1.29)	(0.91,1.50)		
LYs	17.25	20.51	3.26	$365,905	per LY gained
(95% CI)	(8.24,10.25)	(9.19,11.37)	(1.83,5.38)		
evLYG	9.04	11.82	2.78	$428,954	per evLY gained
(95% CI)	(0.39,0.48)	(2438672.49,3141649.71)	(1.62,4.46)		
QALYs	9.04	10.16	1.12	$1,065,484	per QALY gained
(95% CI)	(1325103.29,1929147.97)	(10.40,13.59)	(0.69,1.74)	(0396)	

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Table E10: Probabilistic Results for Voxelotor Compared to Usual Care

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio (Probability cost-effective at $1 million per QALY)	
Total Cost	$1,576,025	$2,992,845	$1,416,820	-	
(95% CI)	($1,331,750,$1,920,072)	($2,656,914,$3,431,558)	($1,305,828,$1,525,508)		
VOC	51.53	50.57	-0.96		

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio (Probability cost-effective at $1 million per QALY)	
(95% CI)	(46.39,58.10)	(33.55,67.13)	(-17.41,14.98)	$1,480,485	per VOC avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
(95% CI)	(0.00,0.00)	(0.00,0.00)	(0.00,0.00)		
LYs	17.18	20.04	2.86	$494,836	per LY gained
(95% CI)	(8.25,10.12)	(9.35,11.57)	(1.54,4.89)		
evLYG	9.10	11.76	2.66	$532,681	per evLY gained
(95% CI)	(0.39,0.48)	(2656914.26, 3431557.97)	(1.58,4.40)		
QALYs	9.10	10.38	1.28	$1,110,073	per QALY gained
(95% CI)	(1331750.41,1920072.19)	(10.38,13.62)	(0.79,2.08)	(0.273)	

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Table E11: Probabilistic Results for L-Glutamine Compared to Usual Care

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio (Probability cost-effective at $1 million per QALY)	
Total Cost	$1,581,946	$1,877,370	$295,423	-	
(95% CI)	($1,332,573,$1,905,731)	($1,547,221,$2,243,407)	($178,263,$375,443)		
VOC	51.66	41.17	-10.50	$28,143	per VOC avoided
(95% CI)	(46.57,58.25)	(31.62,51.12)	(-20.27,-1.64)		
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
(95% CI)	(0.00,0.00)	(0.00,0.00)	(0.00,0.00)		
LYs	17.22	18.93	1.71		

Treatment	Usual Care	Voxelotor	Difference	Incremental cost-effectiveness ratio (Probability cost-effective at $1 million per QALY)	
(95% CI)	(8.25,10.22)	(8.78,10.83)	(0.95,2.69)	$172,438	per LY gained
evLYG	9.14	10.62	1.48	$199,567	per evLYG
(95% CI)	(0.39,0.48)	(1547220.78,2243407.06)	(0.90,2.25)		
QALYs	9.14	9.71	0.58	$511,562	per QALY gained
(95% CI)	(1332573.14,1905731.35)	(9.54,11.82)	(0.34,0.90)	(0.974)	

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Table E12: Probabilistic Results for Crizanlizumab Compared to Usual Care: Health Care Perspective

Treatment	Usual Care	Crizanlizumab	Difference
Total Cost	$1,570,983	$2,732,636	$1,161,652
(95% CI)	($1,320,932,$1,922,402)	($2,410,671,$3,136,811)	($1,069,882,$1,258,745)
VOC	51.38	32.47	-18.91
(95% CI)	(46.42,57.94)	(14.26,50.16)	(-37.19,-1.29)
Hemoglobin (g/dL)	0.00	0.00	0.00
(95% CI)	(0.00-0.00)	(0.00-0.00)	(0.00-0.00)
LYs	17.13	20.47	3.35
(95% CI)	(15.47,19.31)	(18.03,23.04)	(1.75,5.52)
evLYG	8.03	10.87	2.83
(95% CI)	(6.27,9.87)	(8.77,13.17)	(1.54,4.56)
QALYs	8.03	9.04	1.01
(95% CI)	(6.27,9.87)	(7.09,11.11)	(0.55,1.61)

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Table E13: Probabilistic Results for Voxelotor Compared to Usual Care: Health Care Perspective

Treatment	Usual Care	Voxelotor	Difference
Total Cost	$1,591,341	$3,110,575	$1,519,234
(95% CI)	($1,318,768,$1,933,414)	($2,739,570,$3,552,873)	($1,397,365,$1,644,052)
VOC	51.77	51.01	-0.76
(95% CI)	(46.46,57.98)	(34.52,69.19)	(-17.13,15.16)
Hemoglobin (g/dL)	-0.10	1.10	1.20
(95% CI)	(-0.31,0.10)	(0.89,1.31)	(0.91,1.48)
LYs	17.26	20.09	2.83
(95% CI)	(6.38,9.96)	(7.30,11.37)	(1.55,4.73)
evLYG	8.11	10.72	2.61
(95% CI)	(0.31,0.47)	(2739570.12,3552873.24)	(1.52,4.22)
QALYs	8.11	9.23	1.12
(95% CI)	(1318768.33,1933413.61)	(8.67,13.10)	(0.66,1.85)

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Table E14: Probabilistic Results for L-Glutamine Compared to Usual Care: Health Care Perspective

Treatment	Usual Care	L-Glutamine	Difference
Total Cost	$1,581,958	$1,923,307	$341,348
(95% CI)	($1,307,309,$1,913,688)	($1,634,285,$2,273,677)	($306,093,$378,919)
VOC	51.64	41.42	-10.22
(95% CI)	(46.48,58.49)	(31.93,50.50)	(-19.89,-3.17)
Hemoglobin (g/dL)	0.00	0.00	0.00
(95% CI)	(0.00-0.00)	(0.00-0.00)	(0.00-0.00)
LYs	17.21	18.90	1.69
(95% CI)	(15.49,19.50)	(17.04,21.21)	(0.99,2.71)
evLYG	8.08	9.54	1.46
(95% CI)	(6.41,10.07)	(7.77,11.61)	(0.93,2.27)
QALYs	8.08	8.58	0.50
(95% CI)	(6.41,10.07)	(6.83,10.66)	(0.30,0.80)

95%CI: 95% confidence interval, evLYG: equal value life years gained, g/dL: grams per deciliter, LY: life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

Appendix F. Patient Survey Questionnaire

The full survey can be found below.

Thank you for participating in our survey! Please fill out the following questions to the best of your ability. It should take you about 15 minutes to complete.

Sick Cells and the Sickle Cell Disease Association of America (SCDAA) are working with the Institute for Clinical and Economic Review (ICER) to inform the evaluation of the clinical and economic impact of new treatments for sickle cell disease. You can learn more about ICER's review of SCD treatment here.

The survey is only for people living in the United States. All responses are anonymous and will be summarized in ICER's report and public meeting. Survey closes on January 31st, 2020 at 5PM PST.

Please reach out to mjalowsky@sickcells.org with any questions.

1. Which of the following best describes you? **Select one.**

( ) I am living with sickle cell disease

( ) I am a family member or caregiver of someone living with sickle disease

( ) None of the above

Page 2: About You

* 2. How old are you?

```
[                                    ]
```

* 3. What is your gender?

( ) Female

( ) Male

( ) Other (please specify)

```
[                                    ]
```

* 4. Which categories describe you? (Select all that apply)

[ ] Asian or Pacific Islander

[ ] American Indian or Alaskan Native

[ ] Black or African American

[ ] Hispanic, Latinx, or Spanish origin

[ ] Middle Eastern or North African

[ ] White

[ ] Some other race, ethnicity, or origin (please specify)

```
[                                    ]
```

* 5. What is your <u>primary</u> source of health insurance?

○ Commercial health insurance (examples: Blue Cross, United, Kaiser) through work, school, or parents

○ Commercial health insurance (examples: Blue Cross United, Kaiser) through my state exchange program (also known as the Affordable Care Act or "Obamacare")

○ Through my state Medicaid program

○ Through Medicare

○ Through the Veterans Administration (VA) or Tricare

○ I do not currently have insurance

○ I don't know

○ Other (please specify)

[ ]

* 6. In what state do you live?

[⬍]

* 7. Thinking back on **the last week**, what health effects of sickle cell disease have the greatest impact on your life? **Select up to three.**

☐ Acute pain crises

☐ Chronic daily pain, such as joint or hip pain

☐ Fatigue or sleep disturbance

☐ Cognitive impairment (i.e. problems remembering or difficulty with completing complicated tasks)

☐ Strokes

☐ Acute chest syndrome

☐ Iron overload

☐ Damage to heart

☐ Pulmonary hypertension (high blood pressure in the lungs)

☐ Kidney disease

☐ Gallstones

☐ None of the above

☐ Other effects not listed above (please specify)

[ ]

Page 3: Work and Daily Activities

The following questions ask about the effect of sickle cell disease and its complications on your ability to work and 1erform regular activities (such as work around the house, shopping, childcare, exercising, studying, etc.).

 * 8. Are you currently employed (working for pay)?

  ○ Yes

    No (Please describe why you are not currently employed)

The next questions are about **the past seven days**, not including today

* 9. During the past seven days, **how many hours** did you miss from work because of <u>sickle cell disease and its complications</u>?

- Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems.
- Do not include time you missed to participate in this survey.

[   ]

* 10. During the past seven days, **how many hours** did you miss from work because of <u>any other reason</u>, such as vacation, holidays, time off to participate in this survey?

[   ]

* 11. During the past seven days, **how many hours** did you actually work?

[   ]

12. During the past seven days, how much did sickle cell disease and its complications affect your productivity while you were working?

- Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual.
- If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.
- Consider only how much sickle cell disease and its complications affected productivity while you were working.
- If you did not work this week, skip to the next question.

| Sickle cell disease had no effect on my work | _____ | Sickle cell disease completely prevented me from working |

0 1 2 3 4 5 6 7 8 9 10

Use the sliding scale below to choose between 0 to 10.

0   5   10

* 13. During the past seven days, how much did sickle cell disease and its complications affect your ability to do your regular daily activities, other than work at a job?

- By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like.
- If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.
- Consider only how much sickle cell disease and its complications affected your ability to do your regular daily activities, other than work at a job.

| Sickle cell disease had no effect on my work | _____ | Sickle cell disease completely prevented me from working |

0 1 2 3 4 5 6 7 8 9 10

Use the sliding scale below to choose between 0 to 10.

0   5   10

Page 4: Your Pain Experience

* 14. Thinking back on the **last year**, how many pain crises did you experience? Pain crises are episodes of pain that differ from daily baseline pain.

- Include total number of pain crises that were treated <u>at home and/or required medical attention</u> (going to a doctor, emergency room, or hospital).

[   ]

* 15. Thinking back on the **last year**, how many pain crisis events required you to seek medical attention (go to the doctor, emergency room, or hospital) in order to ease your pain?

[   ]

* 16. Thinking about your **most recent pain crisis**, how long did your pain last?

◯ Less than 1 day

◯ 1-2 days

◯ 3-4 days

◯ More than 4 days (please specify how many days)

[   ]

17. During your **most recent pain crisis**, how many days were you unable to do the following?

- For each item, write in <u>the number of missed days.</u>
- If you do not regularly participate in the activity, leave the item blank.
- If you could still participate in the activity and did not need to miss any days, write "0" days.

Go to work	[ ]
Go to school	[ ]
Participate in normal physical activity (go for a walk, walk up a flight of stairs, carry groceries)	[ ]
Participate in normal social	

activities (visit with
family, friends, neighbors,
or religious groups)

* 18. During **the past week**, on average, how would you rate your <u>daily baseline pain</u> on a scale of 0 to 10?

0-10 NUMERIC PAIN RATING SCALE

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

NONE   MILD   MODERATE   SEVERE

Use the sliding scale below to choose between 0 to 10.

0   10

* 19. What treatments have you used <u>in the last month</u> to manage sickle cell disease? ***Select all that apply.***

☐ Hydroxyurea	☐ Crizanlizumab (Adakveo)
☐ Simple Blood transfusions	☐ Over-the-counter pain medicine (such as ibuprofen, Tylenol, or Aleve)
☐ Exchange transfusion (RBC apheresis exchange transfusion)	
☐ Prescription grade L-glutamine (Endari)	☐ Prescription pain medication (such as codeine, morphine, or dilaudid)
☐ Voxelotor (Oxbryta)	☐ Hydration infusions (IV infusion for hydration)
	☐ No treatment
☐ Other (please specify)	

20. On average, how much do you spend **per month** <u>out-of-pocket</u> (such as on co-pays, co-insurance or non-covered services) for sickle cell disease and its complications on the following?

- If you <u>do not use</u> the item, write "N/A"
- If you <u>use the item</u> however <u>do not spend money out-of-pocket</u> on the item, write "0".
- If you use the item and you <u>do not know</u> how much you spent out-of-pocket on the item, write "I do not know."

Medical appointments and hospitalizations related to sickle cell disease	
Medications (both prescription and over the counter)	
Vitamins or nutritional supplements	
Paid caregivers or support services (such as for care in the home, housework, errands, etc.)	
Medical supplies (such as wheelchairs, canes, bandages, wound care, oxygen equipment, etc.)	
Transportation, parking, and other accommodations for medical appointments and hospitalizations (such as meals and child care)	
Pain management techniques (such as massage, yoga, meditation, etc.)	
Mental health services	
Other	

21. Is there anything else you would like us to know about living with sickle cell disease?

Page 2: About You and the Person You Care For

* 22. What is your relationship to the person you care for?

○ They are my child or grandchild   ○ They are my spouse or partner

○   They are my parent or grandparent   ○ I am a paid caregiver

○   They are another family member

○ Other (please specify)

[   ]

* 23. How old is the person you care for?

[   ]

* 24. What is the gender of the person you care for?

○ Female

○ Male

○ Other (please specify)

[   ]

* 25. Which categories describe the person you care for? (Select all that apply)

☐ Asian or Pacific Islander

☐ American Indian or Alaskan Native

☐ Black or African American

☐ Hispanic, Latinx, or Spanish origin

☐ Middle Eastern or North African

☐ White

☐ I do not know or I prefer not to answer

☐ Some other race, ethnicity, or origin (please specify)

[   ]

* 26. What is your <u>primary</u> source of health insurance for the person you care for?

○ Commercial health insurance (examples: Blue Cross, United, Kaiser) through work, school, or parents

○ Commercial health insurance (examples: Blue Cross United, Kaiser) through their state exchange program (also known as the Affordable Care Act or "Obamacare")

○ Through their state Medicaid program

○ Through Medicare

○ Through the Veterans Administration (VA) or Tricare

○ The person I care for does not currently have insurance

○ I don't know

○ Other (please specify)

[   ]

* 27. In what state does the person you care for live?

[▲▼]

* 28. Thinking back on the **last week**, what health effects of sickle cell disease have the greatest impact on the person you care for? *Select up to three.*

☐ Acute pain crises

☐ Chronic daily pain, such as joint or hip pain

☐ Fatigue or sleep disturbance

☐ Cognitive impairment (i.e. problems remembering or difficulty with completing complicated tasks)

☐ Strokes

☐ Acute chest syndrome

☐ Iron overload

☐ Damage to heart

☐ Pulmonary hypertension (high blood pressure in the lungs)

☐ Kidney disease

☐ Gallstones

☐ None of the above

☐ Other effects not listed above (please specify)

[   ]

The following questions ask about the effect of providing care for a person living with sickle cell disease on your ability to work and perform regular activities (such as work around the house, shopping, childcare, exercising, studying, etc).

* 29. Are you currently employed (working for pay)?

◯ Yes

No (Please describe why you are not currently employed)

The next questions are about **the past seven days**, not including today

* 30. During the past seven days, **how many hours** did you miss from work <u>because of time providing care for a person living with sickle cell disease</u>?

  - Include hours you missed on sick days, times you went in late, left early, etc., because of your caregiving activities.
  - Do not include time you missed to participate in this survey.

  [   ]

* 31. During the past seven days, **how many hours** did you miss from work because of <u>any other reason</u>, such as vacation, holidays, time off to participate in this survey?

  [   ]

* 32. During the past seven days, **how many hours** did you actually work?

  [   ]

33. During the past seven days, how much did <u>providing care for a person living with sickle cell disease</u> affect your productivity <u>while you were working</u>?

- Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual.
- If caregiving affected your work only a little, choose a low number. Choose a high number if caregiving affected your work a great deal.
- Consider only how much <u>providing care for a person living with sickle cell disease</u> affected productivity <u>while you were working.</u>
- If you did not work in the past week, skip to the next question.

| Providing care for a person living with sickle cell disease had no effect on my work | _____ | Providing care for a person living with sickle cell disease completely prevented me from doing my work |

0 1 2 3 4 5 6 7 8 9 10

Use the sliding scale below to choose between 0 to 10.

0   5   10

* 34. During the past seven days, how much did <u>providing care for a person living with sickle cell disease</u> affect your ability to do your regular daily activities, <u>other than work at a job</u>?

- By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like.
- If caregiving affected your activities only a little, choose a low number. Choose a high number if caregiving affected your activities a great deal.
- Consider only how much <u>providing care for a person living with sickle cell disease</u> affected your ability to do your regular daily activities, other than work at a job.

| Providing care for a person living with sickle cell disease had no effect on my work | | Providing care for a person living with sickle cell disease completely prevented me from doing my work |

0 1 2 3 4 5 6 7 8 9 10

Use the sliding scale below to choose between 0 to 10.

0   5   10

* 35. Thinking back on the **last year**, how many pain crises did the person you care for experience? Pain crises are episodes of pain that differ from daily baseline pain.

- Include total number of pain crises that were treated <u>at home and/or required medical attention</u> (going to a doctor, emergency room, or hospital).

<div style="border:1px solid #000; height:40px;"></div>

* 36. Thinking back on **the last year**, how many pain crisis events required the person you care for to seek medical attention (go to the doctor, emergency room, or hospital) in order to ease their pain?

<div style="border:1px solid #000; height:40px;"></div>

* 37. Thinking about their **most recent pain crisis**, how long did their pain last?

- ( ) Less than 1 day
- ( ) 1-2 days
- ( ) 3-4 days
- ( ) More than 4 days

* 38. How was their **most recent pain crisis** treated? *Select all that apply.*

- ☐ NSAIDs (such as ibuprofen, ketorolac, diclofenac, Advil or Motrin)
- ☐ Opioid pills (such as codeine, morphine, or dilaudid)
- ☐ IV fluids
- ☐ IV opioids
- ☐ Other (please specify)

<div style="border:1px solid #000; height:40px;"></div>

39. During their **most recent pain crisis**, how many days were they unable to do the following?

- For each item, write in the number of missed days.
- If the person you care for does not regularly participate in the activity, leave the item blank.
- If they could still participate in the activity and did not need to miss any days, write "0."

Go to work

Go to school

Participate in normal physical activity (go for a walk, walk up a flight of stairs, carry groceries)

Participate in normal social activities (visit with family, friends, neighbors, or religious groups)

* 40. During **the past week**, on average, how would you rate the daily baseline pain of the person you care for on a scale of 0 to 10?

0-10 NUMERIC PAIN RATING SCALE

0	1	2	3	4	5	6	7	8	9	10

NONE   MILD   MODERATE   SEVERE

Use the sliding scale below to choose between 0 to 10.

0   10

Page 5: Healthcare Expenses
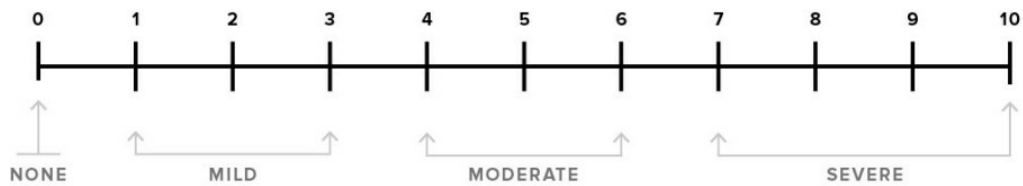
* 41. What treatments has the person you care for used **in the past month** to manage sickle cell disease? *Select all that apply.*

☐ Hydroxyurea	☐ Crizanlizumab (Adakveo)
☐ Simple Blood transfusions	☐ Over-the-counter pain medicine (such as ibuprofen, Tylenol, or Aleve)
☐ Exchange transfusion (RBC apheresis exchange transfusion)	☐ Prescription pain medication (such as codeine, morphine, or dilaudid)
☐ Prescription grade L-glutamine (Endari)	☐ Hydration infusions (IV infusion for hydration)
☐ Voxelotor (Oxbryta)	☐ No treatment
☐ Other (please specify)	☐
	☐

42. On average, how much do you spend **per month** <u>out-of-pocket</u> (such as on co-pays, co-insurance or non-covered services) as a caregiver for a person with sickle cell disease on the following?

- Only include expenses <u>that you pay</u> related to sickle cell disease and its complications.
- If the person with sickle cell disease <u>does not use</u> the item, write "N/A."
- If the person with sickle cell disease <u>uses the item</u> however you <u>do not spend money out-of-pocket</u> on the item, write "0".
- If the person with sickle cell disease uses the item and <u>you do not know</u> how much you spend out-of-pocket on the item, write "I do not know."

Medical appointments and hospitalizations related to sickle cell disease	
Medications (both prescription and over the counter)	
Vitamins or nutritional supplements	
Paid caregivers or support services (such as for care in the home, housework, errands, etc.)	
Medical supplies (such as wheelchairs, canes, bandages, wound care, oxygen equipment, etc.)	
Transportation, parking, and other accommodations for medical appointments and hospitalizations (such as meals and child care)	
Pain management techniques (such as massage, yoga, meditation, etc.)	
Mental health services	
Other	

43. On average **per month**, how much money in lost wages from time off work have you experienced caring for a person with sickle cell disease?

- If you do not work, leave the question blank.
- If you do not experience lost wages, write "0"

44. Is there anything else you would like us to know about living with sickle cell disease?

Appendix G. Real World Evidence Final Protocol

The full protocol can be found below.

Acronym/Title	ICER sickle cell disease (SCD) model inputs
Protocol version and date	V 1.0, 15 January 2020
Study type / Study phase	Observational study
Study Investigator	Brigham Women's Hospital Principle Investigator: Sebastian Schneeweiss, MD, ScD
Country(-ies) of study	United States

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed.
Hence, the appearance of product names without these symbols does not imply that these names are
not protected.

1.   Table of contents

2.   List of abbreviations

AEP	Aetion Evidence Platform®
CCAE	Commercial Claims and Encounters
CKD	Chronic kidney disease
COB	Coordination of Benefits
ER	Emergency room
HbC	hemoglobin C
HbSS	homozygous sickle hemoglobin
ICER	Institute of Clinical and Economic Review
IQR	Interquartile range
MDCR	MarketScan Medicare Supplemental and Coordination of Benefits Database
OLS	Ordinary least squares
SCD	Sickle cell disease
SD	Standard deviation

3.   Rationale and background

A series of analyses using the Aetion Evidence Platform® (AEP) were conducted within a Marketscan dataset to obtain evidence on the characteristics of commercially-insured patients with sickle cell disease (SCD), rates of treatment, rates acute and chronic outcomes, and the costs associated with these outcomes. Results from this analysis were used to inform the Institute for Clinical and Economic Review (ICER) cost-effectiveness model.

4. Research questions and objectives

The objectives of this study are:

To characterize patients with SCD. Specifically,

- To describe baseline patient characteristics including demographics
- To describe rates of acute and chronic clinical outcomes of interest
- To estimate the incidence of chronic outcomes of interest
- To describe rates of treatment, including bone marrow transplant, use of hydroxyurea, and chronic transfusion
- To estimate costs of acute and chronic events of interest

5. Research methods

5.1.1 Study population

The study population was derived from patients with SCD. Patients entered the cohort on their first diagnosis of SCD within all available data (2002 – 2017). The population was restricted to patients with three or more SCD diagnoses during available data (see appendix for further detail), implemented by requiring two additional diagnoses following cohort entry.

As noted below, subsets of this overall SCD population were evaluated for the cost analyses.

5.1.1.1 Cohort subset 1 *(analysis of acute event costs)*

For each acute event of interest, a cohort of patients with SCD and with the event between January 01, 2014 and December 01, 2017 was identified. Only these later years of data (2014 – 2017) were used to obtain more recent and relevant cost estimates. Patients entered the cohort on the acute event date. Only patients with an incident acute event were included; those patients with an event in the 180 days prior to the cohort entry date were excluded. Each patient was included only once, on the first qualifying event.

Patients were required to have at least 30 days of enrollment prior to cohort entry in order to obtain baseline cost estimates. The event-based cohorts were nested within the broader population of patients meeting the sickle cell disease definition.

5.1.1.2 Cohort subset 2 *(analysis of chronic event costs)*

For each chronic event of interest, patients were identified from within a parent population of patients with an SCD diagnosis between January 2014 and December 2016 and at least three diagnoses total during available follow-up. Subjects included patients who were newly diagnosed

with the chronic condition and a risk-set sampled referent group, identified during January 01, 2014 and December 31, 2016.

Patients with chronic conditions were required to be newly-diagnosed with the chronic condition, having no diagnoses in the 180 days prior to the cohort entry date. While this focus on incident patients may have reduced the generalizability, it allowed for clearer temporality between chronic condition status and cost and more valid estimates.

For each patient with the chronic condition, up to three referent patients were risk-set sampled from a pool of potential patients who did not have the chronic condition on the exposed patient's cohort entry date and met the same enrollment, inclusion and exclusion criteria. Risk-set sampled referent patients were assigned the same cohort entry date as the patient with the chronic condition.

Patients were not allowed to be sampled for the referent group if they had the chronic condition on the potential cohort entry date or in the 180 days prior to the potential cohort entry date. In addition, patients were only eligible to be sampled as referent on days they had a prescription, outpatient visit or inpatient visit to ensure they were similar in terms of being engaged with the healthcare system.

5.2   Variables

Refer to

<u>Annex 1: Variable definitions</u> for the definitions of patient characteristics including SCD, study treatment, and outcome events of interest.

5.2.1   Patient characteristics

The following patient characteristics were evaluated on each patient's cohort entry date:

- Age
- Gender
- Geographic region
- Age category (< 2, 2 – 4, 5 – 12, 13 – 18, 18+)
- Age category (<18, 18+)
- Medicare coverage

The presence of specific SCD diagnosis codes were evaluated over all available data for each patient.

- Sickle cell – hemoglobin C (HbC)

- Sickle cell – homozygous sickle hemoglobin (HbSS)

- Sickle cell – thalassemia

- Sickle cell disease - other

5.2.2   Treatment

Treatments of interest were:

- Bone marrow transplant
- Use of hydroxyurea
- Chronic transfusion

The hydroxyurea analysis was restricted to patients with complete prescription information.

5.2.3   Outcomes definition

The following study outcomes are defined below.

5.2.3.1   Acute outcomes for rate estimates

Acute outcomes were:

- Renal infarction (any diagnosis) – inpatient
- Stroke (any diagnosis) – inpatient
- Myocardial infarction (any diagnosis) – inpatient
- Acute chest syndrome (any diagnosis) – emergency room (ER) or inpatient

- Acute pain episode (any diagnosis) – ER or inpatient
- Iron overload episode (chelation treatment preceded by a diagnosis)

5.2.3.2 Chronic outcomes *(first recorded following cohort entry)* for rate estimates

Chronic outcomes were:

- Pulmonary hypertension
- Heart failure
- Opioid dependence
- Nephropathy / chronic kidney disease (CKD)
- Fatigue
- Cognitive impairment

5.2.3.3 Acute outcomes for cost estimates

Costs were estimated for the following acute outcomes:

- Stroke (any diagnosis) – inpatient
- Myocardial infarction (any diagnosis) – inpatient
- Acute chest syndrome (any diagnosis) – ER or inpatient
- Acute pain episode (any diagnosis) – ER or inpatient
- Iron overload episode (chelation treatment preceded by a diagnosis)

Note: Cost analyses were planned for renal infarction, but were not possible due to the small number of patients with an event during the analysis period.

5.3 Data sources

All analyses were performed using de-identified administrative claims data without access to personal identifying information. Study findings contained aggregate data only that could not be used to identify individual patients.

5.3.1 IBM Truven MarketScan

Truven MarketScan Databases

The Truven MarketScan databases capture de-identified, longitudinal, individual-level administrative claims data from the United States. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database. The IBM MarketScan Commercial Claims and Encounters (CCAE) Database contains data from active employees, early retirees, COBRA continuees, and dependents insured by employer-sponsored plans (i.e., individuals not eligible for Medicare). The IBM MarketScan Medicare

Supplemental and Coordination of Benefits (COB) Database (also known as MDCR) is created for Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This database contains predominantly fee-for-service plan data. Among the SCD population, 3% of patients had Medicare coverage.

The following tables of the MarketScan databases were available for analysis: Enrollment Detail, Inpatient Admissions, Inpatient Services, Outpatient Services, Outpatient Pharmaceutical Claims, and Long Term Care. These tables provide information on plan enrollment, healthcare utilization and expenditures, demographics, and integrated records for inpatient events, outpatient events, and pharmacy dispensings. Unless otherwise noted, drug event duration was calculated from the "Days Supply" field, and in cases where this field was 0, the duration was assumed to be 1 day.

Data were available from December 31, 2002 to December 31, 2017, and represent approximately 192 million patients.

5.3.2 General notes on administrative databases

Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically.[1,2] Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information[3] or prescribing records in outpatient medical records.[4] Drugs used during hospital stays are not recorded in this data source. Prescribing information based on physician notes may overestimate actual medication use because up to 50% of prescriptions are never filled at the pharmacy.[5]

5.4 Statistical analysis

5.4.1 Rate of acute outcomes

Rates of acute outcomes were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment or end of data. Death is not captured within Marketscan data, but will trigger disenrollment. The total number of events across the population were counted and divided by total follow-up time. Rates were presented as events per 1000 person-years. Total event counts across the population were also provided.

The iron overload episode analysis was restricted to patients with complete prescription information.

Counts of events during a 1-year period were also calculated. This analysis was restricted to the subset of the population with a full year of follow-up. Mean number of events per patient and standard deviation (SD) was reported for all acute events. In addition, frequencies of counts of acute pain episode during follow-up were reported.

5.4.2 Rates of chronic outcomes *(first recorded occurrence following cohort entry)*

Rates of chronic conditions were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment, end of data, or occurrence of outcome. The rate was calculated as the number of patients with an outcome divided by total follow-up time. Rates were presented as the value per 1000 person-years.

Note: This event rate should not be interpreted as a true incidence rate – refer to incidence analysis in Section 5.4.3.

5.4.3 Incidence of chronic outcome

In order to assess incidence of chronic conditions among patients who did not already have the chronic condition, an analysis was conducted restricted to patients with 180 days of baseline data who did not have the condition of interest recorded during that period. This analysis was conducted within a subset of SCD patients present in the data during 2013 – 2017, with cohort entry set to the first day when the patient had 180 days of prior enrollment data. One limitation is the possibility that 180 days is not a sufficient look-back period for ascertaining the presence of chronic conditions, particularly if the patient had not actively sought care for the condition.

5.4.4 Rates of treatment *(following cohort entry)*

Rates of treatment were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment, end of data, or occurrence of treatment. The rate was calculated as the number of patients with an outcome divided by total follow-up time. Rates were presented as the value per 1000 person-years.

5.4.5 Costs of acute events

Cost analyses were based on paid amounts reported in the Marketscan data. For each acute outcome, incremental costs were estimated during the 14 day period beginning on the acute outcome date (day 0 – 13) and the 14 days following (day 14 – 27). For acute myocardial infarction and stroke, an average 30-day cost during the 28 to 365 days following the event was also provided. All costs were inflated to 2019 US dollars using the Medical Care Services Component of the Consumer Price Index.[6]

Incremental costs were calculated using a pre-post design among patients with the outcome of interest, with each patient serving as his or her own control.[7,8] For each patient, a 14-day and 30-day average baseline cost was estimated using all available data during up to 180 days preceding the acute outcome date. The total cost during the 14 days beginning on the acute event (day 0 – 13) was calculated for each patient. The incremental cost was estimated as the difference between the day 0 – 13 cost and the 14-day average baseline cost. Mean (sd) and median [IQR] incremental cost values were calculated across the population as an estimate of the cost likely attributed to the acute outcome. A similar procedure was used for the day 14 – 27 incremental cost calculation, restricted to

patients who were still in the dataset during this period. For the calculation of 30-day costs during the 28 – 365 days following the acute event, incremental cost was calculated as 30*(total cost during day 28 to day 365 divided by follow-up days during day 28 to day 365) minus the 30-day baseline cost.

Because repeat events and other high cost acute events are modeled, including their costs within the estimated cost of an acute outcome would result in double-counting their costs. To avoid this, follow-up – and the accumulation of costs – was censored on the occurrence of MI, stroke, renal infarction or bone marrow transplant following the acute event date. Patients with these events during the 180 days preceding the acute event date were excluded from the analysis in order to obtain representative baseline cost data. Due to the higher prevalence of acute pain and acute chest syndrome, these events were not explicitly excluded; rather it was assumed that their costs during baseline and follow-up would net out across the population. Follow-up was additionally censored on the end of 365 days, end of data, or disenrollment.

To assess sensitivity of results to extreme cost values, an additional analysis was performed where incremental cost values were Winsorized,[9] using the 5th and 95th percentile of the cost distribution as cut points. These procedure involves replacing cost values below the 5th percentile with the 5th percentile value and values above the 95th percentile with the 95th percentile value. Thus, extreme values are pulled in, but the weight on the tails of the distribution is maintained.

5.4.6 Costs of chronic events

Costs of chronic conditions were estimated by comparing patients with the condition to matched patients without the condition. In order to obtain annual cost estimates, analyses were restricted to the subset of patients with complete 1-year follow-up. Cost analyses were based on paid amounts reported in the Marketscan data during the 1 year follow-up period. All costs were inflated to 2019 US dollars using the Medical Care Services Component of the Consumer Price Index.[6]

The effect of each chronic condition on cost was estimated by fitting an ordinary least squares (OLS) regression model predicting total 1-year cost as a function of the presence of the chronic condition, adjusting for patient characteristics at baseline. Baseline patients' characteristics include demographic factors measured on cohort entry date, health care resource utilization, costs, receipt of SCD treatments, and presence of other chronic conditions and acute outcomes during the 180 days prior to cohort entry.

The following patient characteristics were included in the fully-adjusted analysis:

- Age
- Age categories (<2, 2-4, 5-12, 13-18, 18+)
- Gender
- Region

- Presence of cognitive impairment
- Presence of nephropathy / CKD
- Presence of pulmonary hypertension
- Presence of opioid dependence
- Presence of heart failure
- Presence of fatigue
- Occurrence of iron overload episode
- Occurrence of acute chest syndrome (any dx) - ER or inpatient
- Occurrence of acute pain episode (any dx) - ER or inpatient
- Occurrence of stroke (any dx) - inpatient
- Treatment with chronic transfusion
- Treatment with hydroxyurea
- Number of different prescription filled, at generic entity level
- Total inpatient costs
- Total outpatient costs
- Total pharmacy costs
- Hospitalization
- Number of outpatient visit days
- Number of emergency department visit days
- Number of prescriptions filled

5.4.7   Subgroup analysis

5.4.7.1   Rates of acute and chronic outcomes, incidence of chronic outcomes, and rates of treatment stratified by age

For rates of acute and chronic outcomes of interest, incidence of chronic outcomes, and rates of treatment, results were reported for the overall population and stratified on age group at cohort entry. Age categories were 0 – 1, 2 – 4, 5 – 12, 13 – 18, and 18+. In addition, results were generated for the combined pediatric (age <18) group.

5.4.7.2   Cost of acute events analysis stratified by age

For the cost of acute events analysis, results were stratified on age < 18 vs 18+. Due to small numbers of patients < 18 with myocardial infarction (n = 1), stratified results were not provided for myocardial infarction.

5.4.8 Software

Results were generated using the Aetion Evidence Platform® version r3.18.20191126_1826-0-g7a6bbbef8-dirty. The AEP has been previously validated for a range of studies[10,11] and for predicting clinical trial findings.[12] A full listing of all component software versions can be found in Annex 2: Software Components.

6. References

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Annex 1: Variable definitions

Variables	Algorithm	Source
Disease		
Sickle cell disease	Events occurring in any setting with one of the following diagnoses in any position ICD10 ● D57.0 - Hb-SS disease with crisis ● D57.00 - Hb-SS disease with crisis, unspecified ● D57.01 - Hb-SS disease with acute chest syndrome ● D57.02 - Hb-SS disease with splenic sequestration ● D57.1 - Sickle-cell disease without crisis ● D57.2 - Sickle-cell/Hb-C disease ● D57.20 - Sickle-cell/Hb-C disease without crisis ● D57.21 - Sickle-cell/Hb-C disease with crisis ● D57.211 - Sickle-cell/Hb-C disease with acute chest syndrome ● D57.212 - Sickle-cell/Hb-C disease with splenic sequestration ● D57.219 - Sickle-cell/Hb-C disease with crisis, unspecified ● D57.4 - Sickle-cell thalassemia ● D57.40 - Sickle-cell thalassemia without crisis ● D57.41 - Sickle-cell thalassemia with crisis ● D57.411 - Sickle-cell thalassemia with acute chest syndrome ● D57.412 - Sickle-cell thalassemia with splenic sequestration ● D57.419 - Sickle-cell thalassemia with crisis, unspecified ICD9 ● 282.41 - SICKLE-CELL THALASSEMIA WITHOUT CRISIS ● 282.42 - SICKLE-CELL THALASSEMIA WITH CRISIS ● 282.6 - SICKLE-CELL DISEASE	Reeves et al, 2014[1]

	● 282.60 - SICKLE-CELL DISEASE UNSPECIFIED ● 282.61 - HB-SS DISEASE WITHOUT CRISIS ● 282.62 - HB-SS DISEASE WITH CRISIS ● 282.63 - SICKLE-CELL/HB-C DISEASE WITHOUT CRISIS ● 282.64 - SICKLE-CELL/HB C DISEASE WITH CRISIS ● 282.68 - OTHER SICKLE-CELL DISEASE WITHOUT CRISIS ● 282.69 - OTHER SICKLE-CELL DISEASE WITH CRISIS	
Treatments		
Hydroxyurea	The occurrence of **Prescription Claims** with the following attributes: **- NDC Generic Name** is any of: { "HYDROXYUREA" }	

Transfusion	The occurrence of **Inpatient Service or outpatient event** with the following attributes: – **Procedure Code (Position 1), ICD-10** is any of: { "30230P1", "30240H1", "30240N1", "30243H1", "30230N1", "30233P1", "30230H1", "30243N1", "30243P1", "30233H1", "30233N1", "30240P1" } 30230P1 - Transfusion of Nonautologous Frozen Red Cells into Peripheral Vein, Open Approach 30240H1 - Transfusion of Nonautologous Whole Blood into Central Vein, Open Approach 30240N1 - Transfusion of Nonautologous Red Blood Cells into Central Vein, Open Approach 30243H1 - Transfusion of Nonautologous Whole Blood into Central Vein, Percutaneous Approach 30230N1 - Transfusion of Nonautologous Red Blood Cells into Peripheral Vein, Open Approach 30233P1 - Transfusion of Nonautologous Frozen Red Cells into Peripheral Vein, Percutaneous Approach 30230H1 - Transfusion of Nonautologous Whole Blood into Peripheral Vein, Open Approach 30243N1 - Transfusion of Nonautologous Red Blood Cells into Central Vein, Percutaneous Approach 30243P1 - Transfusion of Nonautologous Frozen Red Cells into Central Vein, Percutaneous Approach 30233H1 - Transfusion of Nonautologous Whole Blood into Peripheral Vein, Percutaneous Approach 30233N1 - Transfusion of Nonautologous Red Blood Cells into	Code search (ICD10)

	Peripheral Vein, Percutaneous Approach
	• 30240P1 - Transfusion of Nonautologous Frozen Red Cells into Central Vein, Open Approach
	– **Procedure Code (Position 1), CPT and HCPC** is any of: { "36440", "36450", "S3906", "P9010", "S9538", "36455", "36430", "P9038", "P9011", "P9022", "P9051", "P9056", "P9057", "P9021", "P9054", "P9058", "P9016" }
	  • 36440 - Push transfusion, blood, 2 years or under / Push transfusion, blood, 2 years or younger
	  • 36450 - Exchange transfusion, blood; newborn
	  • S3906 - TRANSFUSION, DIRECT, BLOOD OR BLOOD COMPONENTS
	  • P9010 - BLOOD (WHOLE), FOR TRANSFUSION, PER UNIT
	  • S9538 - HOME TRANSFUSION OF BLOOD PRODUCT(S); ADMINISTRATIVE SERVICES, PROFESSIONAL PHARMACY SERVICES, CARE COORDINATION AND ALL NECESSARY SUPPLIES AND EQUIPMENT (BLOOD PRODUCTS, DRUGS, AND NURSING VISITS CODED SEPARATELY), PER DIEM / HOME TRANSFUSION OF BLOOD PRODUCT(S); ADMINISTRATIVE SERVICES, PROFESSIONAL PHARMACY SERVICES, CARE COORDINATION AND ALL NECESSARY SUPPLIES AND EQUIPMENT (BLOOD PRODUCTS, DRUGS, AND NURSING VISITS CODED SEPARATELY), PER DIEM
	  • 36455 - Exchange transfusion, blood; other than newborn	

	• 36430 - Transfusion, blood or blood components
	• P9038 - RED BLOOD CELLS, IRRADIATED, EACH UNIT
	• P9011 - BLOOD (SPLIT UNIT), SPECIFY AMOUNT / BLOOD, SPLIT UNIT
	• P9022 - RED BLOOD CELLS, WASHED, EACH UNIT
	• P9051 - WHOLE BLOOD OR RED BLOOD CELLS, LEUKOCYTES REDUCED, CMV-NEGATIVE, EACH UNIT
	• P9056 - WHOLE BLOOD, LEUKOCYTES REDUCED, IRRADIATED, EACH UNIT
	• P9057 - RED BLOOD CELLS, FROZEN/DEGLYCEROLIZED/WASHED, LEUKOCYTES REDUCED, IRRADIATED, EACH UNIT
	• P9021 - RED BLOOD CELLS, EACH UNIT
	• P9054 - WHOLE BLOOD OR RED BLOOD CELLS, LEUKOCYTES REDUCED, FROZEN, DEGLYCEROL, WASHED, EACH UNIT
	• P9058 - RED BLOOD CELLS, LEUKOCYTES REDUCED, CMV-NEGATIVE, IRRADIATED, EACH UNIT
	• P9016 - RED BLOOD CELLS, LEUKOCYTES REDUCED, EACH UNIT
	• **Procedure Code (Position 1), ICD-9** is any of: { "99.03", "99.04", "99.01" }
	    – 99.03 - OTHER TRANSFUSION OF WHOLE BLOOD
	    – 99.04 - TRANSFUSION OF PACKED CELLS
	    – 99.01 - EXCHANGE TRANSFUSION	

Chronic transfusion	A sequence of 3+ transfusion events, with each spaced 2 – 6 weeks apart. The start of the first event was used as the episode start date	Based on a review of treatment patterns and clinical expert(s)[2,3]

Bone marrow transplant	The occurrence of an **Inpatient Service** or **Outpatient** event with the following attributes:
	• **Procedure Code (Position 1), ICD-10** is any of: { "30230G2", "30230G3", "30230G4", "30233G2", "30233G3", "30233G4", "30240G2", "30240G3", "30240G4", "30243G2", "30243G3", "30243G4", "30250G1", "30253G1", "30260G1", "30263G1" }
	    o 30230G2 - Transfusion of Allogeneic Related Bone Marrow into Peripheral Vein, Open Approach
	    o 30230G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Peripheral Vein, Open Approach
	    o 30230G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Peripheral Vein, Open Approach
	    o 30233G2 - Transfusion of Allogeneic Related Bone Marrow into Peripheral Vein, Percutaneous Approach
	    o 30233G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Peripheral Vein, Percutaneous Approach
	    o 30233G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Peripheral Vein, Percutaneous Approach
	    o 30240G2 - Transfusion of Allogeneic Related Bone Marrow into Central Vein, Open Approach
	    o 30240G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Central Vein, Open Approach
	    o 30240G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Central Vein, Open Approach
		American Society for Blood and Marrow Transplantation[4]

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    ◦ 30243G2 - Transfusion of Allogeneic Related Bone Marrow into Central Vein, Percutaneous Approach

    ◦ 30243G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Central Vein, Percutaneous Approach

    ◦ 30243G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Central Vein, Percutaneous Approach

    ◦ 30250G1 - Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Open Approach

    ◦ 30253G1 - Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Percutaneous Approach

    ◦ 30260G1 - Transfusion of Nonautologous Bone Marrow into Central Artery, Open Approach

    ◦ 30263G1 - Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach

- **Procedure Code (Position 1), ICD-9** is any of: { "41.02", "41.03" }

    ◦ 41.02 - ALLOGENEIC BONE MARROW TRANSPLANT WITH PURGING

    ◦ 41.03 - ALLOGENEIC BONE MARROW TRANSPLANT WITHOUT PURGING

- **Procedure Code (Position 1), CPT and HCPC** is any of: { "38240", "38243", "38242" }

    ◦ 38240 - Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic / Bone marrow or blood-derived peripheral stem cell transplantation; allogenic / Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

    ◦ 38243 - Hematopoietic progenitor cell (HPC); HPC boost

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	o 38242 - Allogeneic lymphocyte infusions / Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions	
Ischemia-related outcomes: acute		
Acute pain episode	Events occurring in an inpatient or ER setting with any diagnosis of: ICD9: 282.42 - Sickle-cell thalassemia with crisis 282.62 - Hb-SS disease with crisis 282.64 - Sickle-cell/Hb-C disease with crisis 282.69 - Other sickle-cell disorders with crisis, unspecified ICD10: D57.00 - Hb-SS disease with crisis, unspecified D57.219- Sickle-cell/Hb-C disease with crisis, unspecified D57.419 - Sickle-cell thalassemia with crisis, unspecified D57.819 - Other sickle-cell disorders with crisis, unspecified	Shah et al, 2019[5] Bernard et al, 2008[6]
Acute chest syndrome	Events occurring in an inpatient or ER setting with any diagnosis of: ICD10: D57.211 - Sickle-cell /Hb-C disease with acute chest syndrome D57.01 - Hb-SS disease with acute chest syndrome D57.411 - Sickle-cell thalassemia with acute chest syndrome D57.811 - Other sickle-cell disorders with acute chest syndrome ICD9: 517.3 - Acute chest syndrome	Agarwal et al, 2018[7] (ICD9) Code search (ICD10)
Myocardial infarction	Events occurring in an inpatient setting with any diagnosis of:	Kiyota Y et al, 2004[8]

	ICD9: 410.x0 - Acute myocardial infarction, episode of care unspecified ICD9: 410.x1 - Acute myocardial infarction, initial episode of care ICD10: I21.x - Acute myocardial infarction I22.x - Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	Code search (ICD10)
Renal infarction	Events occurring in an inpatient setting with any diagnosis of: ICD10: N28.0 - Ischemia and infarction of kidney ICD9: 593.81 - vascular disorders of the kidney	Code search (ICD10)
Stroke (ischemic or hemorrhagic)	Events occurring in an inpatient setting with any diagnosis of: ICD9: 430.x - Subarachnoid hemorrhage 431.x - Intracerebral hemorrhage 433.x1 - Occlusion and stenosis of precerebral arteries, with infarct 434.x1 - Occlusion of cerebral arteries,with infarct 436.x - Acute, but ill-defined, cerebrovascular disease ICD10: I60.x - Nontraumatic subarachnoid hemorrhage I61.x - Nontraumatic intracerebral hemorrhage 162.x - Other and unspecified nontraumatic intracranial hemorrhage I63.xx - Cerebral infarction	Kumamaru et al, 2004 (ICD9)[9] Code search (ICD10)
Ischemia-related outcomes: chronic		
Opioid tolerance / dependence	Events occurring in an any setting with any diagnosis of: ICD-9: 304.00 - 304.03 - Opioid dependence 304.70–73 - Opioid dependence with other drug dependence	Agarwal et al, 2018 (ICD9)[10] Code search (ICD10)

	<u>ICD-10:</u> F11.2x - Opioid dependence	
Pulmonary hypertension	Events occurring in an any setting with any diagnosis of: <u>ICD10:</u> I27.0x - primary pulmonary hypertension I27.2x - secondary pulmonary hypertension I27.81 - Cor pulmonale (chronic) (due to pulmonary hypertension) I27.9 - Pulmonary heart disease, unspecified (resulting from pulmonary hypertension) <u>ICD9:</u> 416.0 - primary pulmonary hypertension 416.8 - Other chronic pulmonary heart diseases (including secondary pulmonary hypertension) 416.9 - Chronic pulmonary heart disease, unspecified (heart disease resulting from pulmonary hypertension)	Agarwal et al, 2018 (ICD9)[10] Code search (ICD10)
Heart failure	Events occurring in an any setting with any diagnosis of: <u>ICD9:</u> 428.xx - heart failure <u>ICD10:</u> I50 - heart failure	Brophy et al, 2004 (ICD9)[11] Code search (ICD10)
Nephropathy, chronic kidney disease	Events occurring in an any setting with any diagnosis of: ICD9: 585.x - chronic kidney disease 586, 593.9 - unspecified kidney failure 580.x - acute glomerulonephritis 582.x - chronic glomerulonephritis (nephritic syndrome) 250.4x, 249.4x - diabetes with renal manifestations 583.x -nephritis and nephropathy not specified as acute or chronic 581.x - nephrotic syndrome	Young et al, 2008 (ICD9)[12] Glasheen et al, 2017 (ICD10)[13]

	ICD10: N18.x - chronic kidney disease N19 - unspecified kidney failure N00.x - acute glomerulonephritis N03.x -chronic glomerulonephritis (nephritic syndrome) N05.x - nephritis and nephropathy not specified as acute or chronic E08.2x - Diabetes mellitus due to underlying condition with kidney complications E09.2x - Drug or chemical induced diabetes mellitus with kidney complications E10.2x - Type 1 diabetes mellitus with kidney complications E11.2x - Type 2 diabetes mellitus with kidney complications E13.2 - Other specified diabetes mellitus with kidney complications N04.x - nephrotic syndrome	
Neurocognitive impairment	Events occurring in an any setting with any diagnosis of: ICD9 331.83 - MILD COGNITIVE IMPAIRMENT SO STATED 780.93 - MEMORY LOSS 438.0 - COGNITIVE DEFICITS 294.9 - UNSPECIFIED PERSISTENT MENTAL DISORDERS DUE TO CONDITIONS CLASSIFIED ELSEWHERE 799.5 - SIGNS AND SYMPTOMS INVOLVING COGNITION 799.51 - ATTENTION OR CONCENTRATION DEFICIT 799.52 - COGNITIVE COMMUNICATION DEFICIT 799.53 - VISUOSPATIAL DEFICIT 799.54 - PSYCHOMOTOR DEFICIT 799.55 - FRONTAL LOBE AND EXECUTIVE FUNCTION DEFICIT	Amra S et al, 2017[14] and code search (ICD10)

| | 799.59 - OTHER SIGNS AND SYMPTOMS INVOLVING COGNITION 290 - DEMENTIAS 290.0 - SENILE DEMENTIA UNCOMPLICATED 290.1x - PRESENILE DEMENTIA 290.2x - SENILE DEMENTIA WITH DELUSIONAL OR DEPRESSIVE FEATURES 290.3 - SENILE DEMENTIA WITH DELIRIUM 290.4x - VASCULAR DEMENTIA 291.2 - ALCOHOL-INDUCED PERSISTING DEMENTIA 292.82 - DRUG-INDUCED PERSISTING DEMENTIA 294.1x - DEMENTIA IN CONDITIONS CLASSIFIED ELSEWHERE 294.2x - DEMENTIA UNSPECIFIED 331.1 - FRONTOTEMPORAL DEMENTIA 331.19 - OTHER FRONTOTEMPORAL DEMENTIA 331.82 - DEMENTIA WITH LEWY BODIES
ICD10 I69.11 - Cognitive deficits following nontraumatic intracerebral hemorrhage I69.01 - Cognitive deficits following nontraumatic subarachnoid hemorrhage I69.91 - Cognitive deficits following unspecified cerebrovascular disease I69.21 - Cognitive deficits following other nontraumatic intracranial hemorrhage I69.31 - Cognitive deficits following cerebral infarction I69.81 - Cognitive deficits following other cerebrovascular disease G31.83 - Dementia with Lewy bodies G31.84 - Mild cognitive impairment, so stated | |

	• R41 - Other symptoms and signs involving cognitive functions and awareness • R41.0 - Disorientation, unspecified • R41.1 - Anterograde amnesia • R41.2 - Retrograde amnesia • R41.3 - Other amnesia • R41.4 - Neurologic neglect syndrome • R41.8 - Other symptoms and signs involving cognitive functions and awareness • R41.81 - Age-related cognitive decline • R41.82 - Altered mental status, unspecified • R41.83 - Borderline intellectual functioning • R41.84 - Other specified cognitive deficit • R41.840 - Attention and concentration deficit • R41.841 - Cognitive communication deficit • R41.842 - Visuospatial deficit • R41.843 - Psychomotor deficit • R41.844 - Frontal lobe and executive function deficit • R41.89 - Other symptoms and signs involving cognitive functions and awareness • R41.9 - Unspecified symptoms and signs involving cognitive functions and awareness • F01 - Vascular dementia • F01.5 - Vascular dementia • F01.50 - Vascular dementia without behavioral disturbance • F01.51 - Vascular dementia with behavioral disturbance • F02 - Dementia in other diseases classified elsewhere • F02.8 - Dementia in other diseases classified elsewhere • F02.80 - Dementia in other diseases classified elsewhere without behavioral disturbance • F02.81 - Dementia in other diseases classified elsewhere with behavioral disturbance	

	• F03 - Unspecified dementia • F03.9 - Unspecified dementia • F03.90 - Unspecified dementia without behavioral disturbance • F03.91 - Unspecified dementia with behavioral disturbance	
Anemia-related outcomes: acute		
Acute pain syndrome	(see above)	
Acute chest syndrome	(see above)	
Iron overload episode	Defined as chelation, with an iron overload diagnosis during the past 60 days. Chelation drug prescriptions within 180 days of one another were considered part of the same episode.	Clinical expert(s) and assumptions
Iron Overload Due to pRBCs	Events in any setting with a primary diagnosis of: Hemochromatosis due to repeat transfusions ICD10 E83.111 ICD9 275.02	Code search (ICD10)
Use of chelation drugs	Use of iron chelation drug - "DEFEROXAMINE MESYLATE", "DEFERASIROX", "DEFERIPRONE"	
Stroke	(see above)	
Anemia-related outcomes: chronic		
Opioid tolerance / dependence	(see above)	
Pulmonary	(see above)	

hypertension		
Heart failure	(see above)	
Nephropathy, chronic kidney disease	(see above)	
Neurocognitive impairment	(see above)	
Fatigue	ICD10 • G93.3 - Postviral fatigue syndrome • R53.0 - Neoplastic (malignant) related fatigue • R53.1 - Weakness • R53.81 - Other malaise • R53.82 - Chronic fatigue, unspecified • R53.83 - Other fatigue ICD9 • 780.7 - MALAISE AND FATIGUE • 780.71 - CHRONIC FATIGUE SYNDROME • 780.79 - OTHER MALAISE AND FATIGUE	U.S. Agency for Healthcare Research and Quality. Clinical Classifications Software (CCS), 2018.[15]

Annex 2: Software Components

Package	Version
R	3.4.2
Formula	1.2.2
Hmisc	4.0.3
RColorBrewer	1.1.2
Rcpp	0.12.13
RcppArmadillo	0.8.100.1.0
SparseM	1.77
TH.data	1.0.8
acepack	1.4.1
aetionstats	2.0
colorspace	1.3.2
dichromat	2.0.0
digest	0.6.12
epitools	0.5.10
forecast	8.2
fracdiff	1.4.2
ggplot2	2.2.1
gridExtra	2.3
gtable	0.2.0
jsonlite	1.5
labeling	0.3
latticeExtra	0.6.28
magrittr	1.5
metafor	2.0.0
multcomp	1.4.8
munsell	0.4.3
mvtnorm	1.0.6
plyr	1.8.4
polspline	1.1.12
proto	0.3-10
quadprog	1.5.5
quantreg	5.34
reshape	0.8.7
reshape2	1.4.2
rms	5.1.1
sandwich	2.4.0
scales	0.5.0

stringi	1.1.6
stringr	1.2.0
timeDate	3042.101
tseries	0.10.42
zoo	1.8.0

Annex 3: Annex References

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[14] Amra S, O'Horo JC, Singh TD, et al. Derivation and validation of the automated search algorithms to identify cognitive impairment and dementia in electronic health records. J Crit Care. 2017 Feb;37:202-205. doi: 10.1016/j.jcrc.2016.09.026.

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